Date of Approval: June 23, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-337

RECUVYRA

Fentanyl

Transdermal Solution

Dogs

For the control of postoperative pain associated with surgical procedures in dogs.

Sponsored by:

Nexcyon Pharmaceuticals, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-337
B. Sponsor:	Nexcyon Pharmaceuticals, Inc. 505 S. Rosa Rd., suite 124, Madison, Wisconsin 53719 Drug Labeler Code: 050929
C. Proprietary Names:	RECUVYRA
D. DEA Schedule:	RECUVYRA (fentanyl) Transdermal Solution contains fentanyl, a high concentration mu opioid receptor agonist, and is a Class II controlled substance.
E. Established Names:	Fentanyl
F. Pharmacological Category:	Opioid analgesic
G. Dosage Form:	Transdermal Solution
H. Amount of Active Ingredient:	50 mg/mL
I. How Supplied:	RECUVYRA (fentanyl) Transdermal Solution is supplied in 10 mL amber-colored glass vials (50 mg fentanyl/mL). Each vial is supplied with a purpose-designed needleless adaptor, syringes, and applicator tips.
J. How Dispensed:	Rx

K. Dosage:

The dosage of RECUVYRA is 1.2 mg/lb (2.7 mg/kg) applied topically to the dorsal scapular area 2 to 4 hours prior to surgery. A single application provides analgesia for 4 days. Use the provided syringe and applicator tips.

RECUVYRA dose (1.2 mg/lb; 2.7 mg/kg) in mL based on body weight

Pounds of body weight	Dose (mL)	Kilograms of body weight
6 to 9.3*	0.2	2.7 to 4.2
9.4 to 13.4	0.3	4.3 to 6.1
13.5 to 17.6	0.4	6.2 to 8
17.7 to 21.8	0.5	8.1 to 9.9
21.9 to 25.9	0.6	10 to 11.7
26 to 30.1	0.7	11.8 to 13.6
30.2 to 34.3	0.8	13.7 to 15.5
34.4 to 38.4	0.9	15.6 to 17.4
38.5 to 42.6	1	17.5 to 19.3
42.7 to 46.8	1.1	19.4 to 21.2
46.9 to 50.9	1.2	21.3 to 23.1
51 to 55.1	1.3	23.2 to 25
55.2 to 59.3	1.4	25.1 to 26.9
59.4 to 63.4	1.5	27 to 28.8
63.5 to 67.6	1.6	28.9 to 30.6
67.7 to 71.8	1.7	30.7 to 32.5
71.9 to 75.9	1.8	32.6 to 34.4
76 to 80.1	1.9	34.5 to 36.3
80.2 to 84.3	2	36.4 to 38.2
84.4 to 88.4	2.1	38.3 to 40.1
88.5 to 92.6	2.2	40.2 to 42
92.7 to 96.8	2.3	42.1 to 43.9
96.9 to 100.9	2.4	44 to 45.8
101 to 105.1	2.5	45.9 to 47.7
105.2 to 109.3	2.6	47.8 to 49.6
109.4 to 113.4	2.7	49.7 to 51.4
113.5 to 117.6	2.8	51.5 to 53.3
117.7 to 121.8	2.9	53.4 to 55.2
121.9 to 125	3	55.3 to 57

* RECUVYRA cannot be accurately dosed in dogs less than 6 pounds of body weight. The average dose in each weight band is approximately 2.7 mg/kg, except for the lowest weights, that average slightly higher.

Apply up to ½ mL onto the skin without moving the applicator tip. If the calculated volume is greater than ½ mL, reposition the applicator tip at least 1 inch from the initial site and apply up to ½ mL. Repeat the reposition and application steps until the entire calculated volume has been applied to the dog. Restrain

the dog for a full 2 minutes and avoid contact with the application site for 5 minutes to allow complete drying of the solution (SEE INSTRUCTIONS FOR USE).

L. Route of Administration: Topical

M. Species: Dogs

N. Indication: For the control of postoperative pain associated with surgical procedures in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

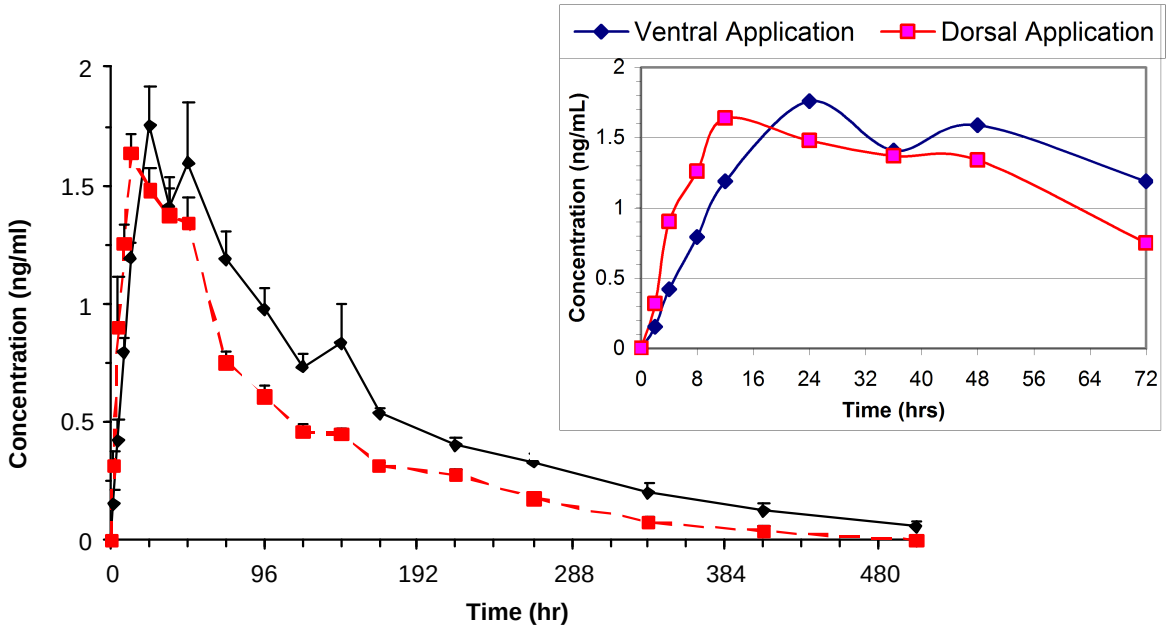
Results from published studies in dogs associated fentanyl plasma concentrations ≥1 ng/mL with clinical analgesia during the postsurgical period. In one study, transdermal fentanyl was compared to intramuscular (IM) oxymorphone following ovariohysterectomy (Kyles 1998). In this study, plasma fentanyl concentrations were measured from just before surgery to 24 hours after surgery, and averaged 1.2 ng/mL. The authors stated that transdermal fentanyl provided similar analgesia to IM oxymorphone. A second study compared transdermal fentanyl to epidural morphine in dogs undergoing major orthopedic surgery (Robinson 1999). Plasma fentanyl concentrations ranged between 0.5-1.0 ng/mL postoperatively, and analgesia was comparable between the two drugs.

A pilot study in dogs (Study T8F1090406) identified unacceptable sedative effects with doses >2.6 mg/kg transdermal fentanyl. Doses of 0, 0.33, 0.65, 1.3, 2.6, and 3.9 mg/kg (n=8 dogs in each group) were applied approximately 12 hours prior to anterior cruciate ligament (ACL) transection surgery. Pain was assessed by a single, masked observer twice daily for two days postoperatively using a visual analog scale (VAS). VAS analgesia scores did not correlate with dose or fentanyl plasma concentrations. Results showed a marked variability (between and within subjects) in fentanyl plasma concentrations, regardless of dose. Plasma concentrations remained above 1 ng/mL for the 2.6 and 3.9 mg/kg doses over the 50 hour observation period. Effects on rectal temperature (decreases), feces presence (decreases), feed intake (decreases), and sedation (increases) were dose related with less acceptable effects noted at the 3.9 mg/kg dose.

A single dose of 2.6 mg/kg transdermal fentanyl was chosen for further investigation in the canine effectiveness field study.

To reduce the time interval between drug administration and surgery, the site of administration chosen for the clinical field trial was the dorsal scapular region. The results of a pharmacokinetic application site study (021591) showed that administration to the dorsal scapular region allows for a more rapid rise and decline in fentanyl plasma concentrations as compared to that seen when fentanyl transdermal solution is applied to the ventral abdominal region (Figure 1).

Figure 1: Influence of site of fentanyl transdermal solution administration on plasma fentanyl concentrations. The inserted graph shows expanded results during the initial 72 hours.



LITERATURE REFERENCES:

Kyles AE, et al. Research in Veterinary Science. Comparison of transdermal fentanyl and intramuscular oxymorphone on post-operative behavior after ovariohysterectomy in dogs. 1998, 65:245-251.

Robinson TM, et al. Journal of the American Animal Hospital. A comparison of transdermal fentanyl versus epidural morphine for analgesia in dogs undergoing major orthopedic surgery. 1999, 35:95-100.

B. Substantial Evidence

1. Type of Study: Field Study Postoperative Pain Evaluation of a Topical Fentanyl Solution following Cruciate Repair Surgery in Dogs

   a. Title: ARDG01-C-01: Clinical Study: Postoperative Pain Evaluation of a Topical Fentanyl Solution following Cruciate Repair Surgery in Dogs

Table 1: Investigators and Study Locations:

LeeAnn Blackford, DVM, DACVS Knoxville, TN	Todd Gauger, DVM Norway, ME
Jack Gallagher, DVM, DACVS Cary, NC	Samuel Geller, VMD Quakertown, PA
John Mauterer, DVM, DACVS Mandeville, LA	Stephan Ladd, DVM Nashville, TN
David Lukof, VMD Harleysville, PA	Andrew Pickering, DVM Terre Haute, IN
John T. Peacock, DVM Memphis, TN	John Stephan, DVM, MS, DACVS Indianapolis, IN
Steven A. Martinez, DVM, MS, DACVS Pullman, WA	

b. Study Design: This was an active controlled, double-masked, multi-centered field study. The objective was to evaluate the clinical effectiveness and safety of RECUVYRA following orthopedic surgery in dogs.

1. Animal Details:

Two hundred and fifty-one (251) client-owned animals were enrolled and received at least one treatment in this study. No more than 40% of all valid cases were provided from any one study site. Dogs were 6 months or older and weighed $\geq$6 pounds at the time of treatment. Both intact and castrated males and intact and ovariohysterectomized females were enrolled.

Animals enrolled in the study included 107 males and 144 females. Of these, 14 were intact males, 93 were castrated males, 4 were intact females, and 140 were spayed females, ranging in age from 0.7 – 13 years. Approximately 69% of the dogs were purebred. About half of the dogs (51%) received cruciate repair via tibial plateau leveling osteotomy (TPLO). Another 39% were repaired by fabellar suture and the remaining 18% were repaired by tibial tuberosity advancement (TTA).

2. Inclusion/Exclusion Criteria and Post-Inclusion Removal Criteria:
A dog was eligible for inclusion in the study if:
   a) it met the animal details criteria above.
   b) it was presented for cranial or caudal cruciate ligament repair to be conducted via arthrotomy.
   c) it had no clinically relevant medical abnormalities detected on hematology or serum chemistry, or physical examination (judged by the Investigator to conflict with the ability of the patient to undergo surgery, dosing, or study response measurements).
   d) it had no history of seizures.
   e) it had a score of P1 or P2 for the American Society of Anesthesiologists (ASA) system.

f) the Owner had been informed of risks and had given informed consent to include the dog in the study by signing the Owner Consent Form, and stated that the dog was current on immunizations as required by local and/or state authorities.

A dog was excluded from the study if it:

a) had not met the inclusion criteria above.
b) exhibited an extremely fractious nature.
c) was pregnant, suspected to be pregnant, or lactating or was a male intended for breeding.
d) had received short-acting systemic corticosteroids within the last 14 days.
e) had received non-steroidal anti-inflammatory drugs (NSAIDs) within 24 hours prior to surgery.
f) had received long-acting corticosteroids within the last 30 days.
g) had another orthopedic, neurological, or uncontrolled systemic disorder which required medical attention.
h) had orthopedic surgery within the last 6 months.
i) had a known sensitivity to opioids, NSAIDs, or to any of the anesthetic articles to be used in the study.

Any dog which required pain intervention was removed from the study. Any dog removed from the study remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

3. Application Site Preparation: If the haircoat allowed direct contact of the applicator tips to the skin, no specific hair clipping or preparation was necessary. For double coated dogs such as Siberian Huskies, where the applicator tips could not directly deposit RECUVYRA onto the skin, clipping the application site was necessary. To maintain masking, the decision and actual clipping of the application site was done at the time of the pre-surgical physical examination without knowledge of the dog's eventual treatment group assignment.

4. Drug Administration: Dogs randomized to RECUVYRA received a single, dermal, topical application on the dorsal scapular area approximately 2 – 4 hours prior to surgery according to the following dosing table:

Table 2: Dose in mL by body weight

Body Weight		
Lb	Kg	Dose (mL)
6.0 to 9.3	3.0 to 4.2	0.2
9.4 to 13.4	4.3 to 6.1	0.3
13.5 to 17.6	6.2 to 8.0	0.4
17.7 to 21.8	8.1 to 9.9	0.5
21.9 to 25.9	10.0 to 11.7	0.6
26.0 to 30.1	11.8 to 13.6	0.7
30.2 to 34.3	13.7 to 15.5	0.8
34.4 to 38.4	15.6 to 17.4	0.9
38.5 to 42.6	17.5 to 19.3	1.0
42.7 to 46.8	19.4 to 21.2	1.1
46.9 to 50.9	21.3 to 23.1	1.2
51.0 to 55.1	23.2 to 25.0	1.3
55.2 to 59.3	25.1 to 26.9	1.4
59.4 to 63.4	27.0 to 28.8	1.5
63.5 to 67.6	28.9 to 30.6	1.6
67.7 to 71.8	30.7 to 32.5	1.7
71.9 to 75.9	32.6 to 34.4	1.8
76.0 to 80.1	34.5 to 36.3	1.9
80.2 to 84.3	36.4 to 38.2	2.0
84.4 to 88.4	38.3 to 40.1	2.1
88.5 to 92.6	40.2 to 42.0	2.2
92.7 to 96.8	42.1 to 43.9	2.3
96.9 to 100.9	44.0 to 45.8	2.4
101.0 to 105.1	45.9 to 47.7	2.5
105.2 to 109.3	47.8 to 49.6	2.6
109.4 to 113.4	49.7 to 51.4	2.7
113.5 to 117.6	51.5 to 53.3	2.8
117.7 to 121.8	53.4 to 55.2	2.9
121.9 to 125.0	55.3 to 57.0	3.0

To prevent direct contact with human skin, latex or nitrile gloves, protective glasses and a laboratory coat were worn when handling and/or applying the solution. The applicator tips were placed directly onto the skin in the dorsal scapular area, making sure that tips were in direct contact with the skin. Up to ½ mL was applied onto the skin without moving the applicator tip. The applicator tip was then re-positioned at least 1 inch from the initial site and up to ½ mL was applied. The reposition and application steps were repeated until the entire volume was applied to the dog. The dog was restrained for approximately 2 minutes and no contact was made with the site for 5 minutes following application.

5. Active Control Veterinary Product: The active control product was oxymorphone hydrochloride. For dogs randomized to the control group, oxymorphone hydrochloride was administered subcutaneously to the dorsal scapular region 2 – 4 hours prior to surgery, at the time of

extubation, and every 6 hours through and including 90 hours (+ 1 hour) post-extubation. To maintain masking, dogs in the RECUVYRA group received a "mock dose" (physical handling of dogs similar to a subcutaneous injection without any treatment or injection) at the time of extubation and every 6 hours through and including 90 hours (+ 1 hour) post-extubation. The amount of the oxymorphone hydrochloride administered at each dosing period was determined from the table below.

Table 3: Oxymorphone Dosing Table

Body Weight (lbs)	Dosage (mLs)*
5 to 15	1.5
≥15 to 30	3.0
≥30 to 60	4.5
Over 60	6.0

*The dosing table reflects converted doses using an oxymorphone concentration of 1 mg/mL (OPANA). Doses are equivalent to the veterinary dosing table (NUMORPHAN) that is based on a 1.5 mg/mL concentration of oxymorphone.

6. Opioid Reversal: If at any time during the study, a dog showed severe adverse reactions consistent with opioid intoxication (such as non-responsive unconsciousness, seizure, marked abdominal breathing), an intravenous dose of naloxone hydrochloride (0.4 mg/mL solution at a dose level of 0.04 mg/kg) was administered. If clinical reversal was not observed after 2 to 3 minutes, administration of naloxone (at the same dose level) was repeated. Any dog requiring reversal with naloxone was considered a treatment failure for statistical analyses, but remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

7. Anesthesia: Anesthetic protocols were similar across all clinics in that dogs were anesthetized using a combination of the following agents according to the veterinarian's preference:

   Anesthetic Premedication:
   - i. glycopyrrolate
   - ii. acepromazine
   - iii. atropine
   - iv. midazolam
   - v. diazepam

Anesthetic Induction:

i. propofol
ii. thiopental
iii. ketamine/diazepam
iv. tiletamine/zolazepam

Anesthetic Maintenance

i. nitrous oxide
ii. isoflurane
iii. sevoflurane

8. Measurements and Observations:

Physical examinations: A physical examination, including blood samples for serum chemistry and hematology was performed for all candidate dogs up to Day -1. A termination physical examination, including blood samples, was conducted on Day 4. For dogs allotted to the RECUVYRA group, a single blood sample for fentanyl assay was randomly collected from Day 0 through Day 4.

Pain assessment: Dogs were assessed for pain using the modified Glasgow Composite Pain Scale (GCPS, see below) by a trained observer at the following time points: prior to treatment (up to Day -1 or on Day 0); Day 0 - approximately 1, 2, 4, 6, 8, and 12 hours post-extubation; Day 1 – approximately 24 hours post initial treatment then 6 – 8 hours later; Day 2 – approximately 48 hours post initial treatment then 6 – 8 hours later; Day 3 – approximately 72 hours post initial treatment then 6 – 8 hours later; and Day 4 – approximately 96 hours post initial treatment. For each dog, pain assessments were made by the same person. Dogs with a score of ≥ 8 on the GCPS were administered an NSAID supplemental analgesic. Any dog requiring supplemental analgesia was considered a treatment failure for statistical analyses, but remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

The computation of the composite pain score was based on an acceptable modification (deletion of Lameness under section B) of the Glasgow Composite Pain Scale (University of Glasgow, Facility of Veterinary Medicine, Pain and Welfare Research Group; Morton, Reid, Scott, Holton & Nolan. Application of a scaling model to establish & validate an interval level pain scale for assessment of acute pain in dogs; 2005, AmJVetRes 66, 2154-2164).

Glasgow Composite Pain Scale Form (Note: Lameness section B deleted):

A. Look at dog in kennel. Is the dog:

(i)	(ii)
0 Quiet	0 Ignoring any wound or painful area
1 Crying or whimpering	1 Looking at wound or painful area
2 Groaning	2 Licking wound or painful area
3 Screaming	3 Rubbing wound or painful area
	4 Chewing wound or painful area

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it:

(iii)	
0	Do nothing
1	Look round
2	Flinch
3	Growl or guard area
4	Snap
5	Cry

D. Overall: Is the dog:

(iv)	(v)
0 Happy and content or bouncy	0 Comfortable
1 Quiet	1 Unsettled
2 Indifferent or non-responsive to surroundings	2 Restless
3 Nervous or anxious or fearful	3 Hunched or tense
4 Depressed or non-responsive to stimulation	4 Rigid

Sedation: Prior to pain assessments, each dog was assessed for sedation according to the following scale:

Sedation Score:

0 - No Sedation Present
1 - Slight Sedation - almost normal; able to stand easily, but appears somewhat fatigued, subdued, or somnolent.
2 - Moderate Sedation - able to stand but prefers to be recumbent; sluggish; ataxic or uncoordinated.
3 - Profound Sedation - unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency.
4 - Unresponsive - in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

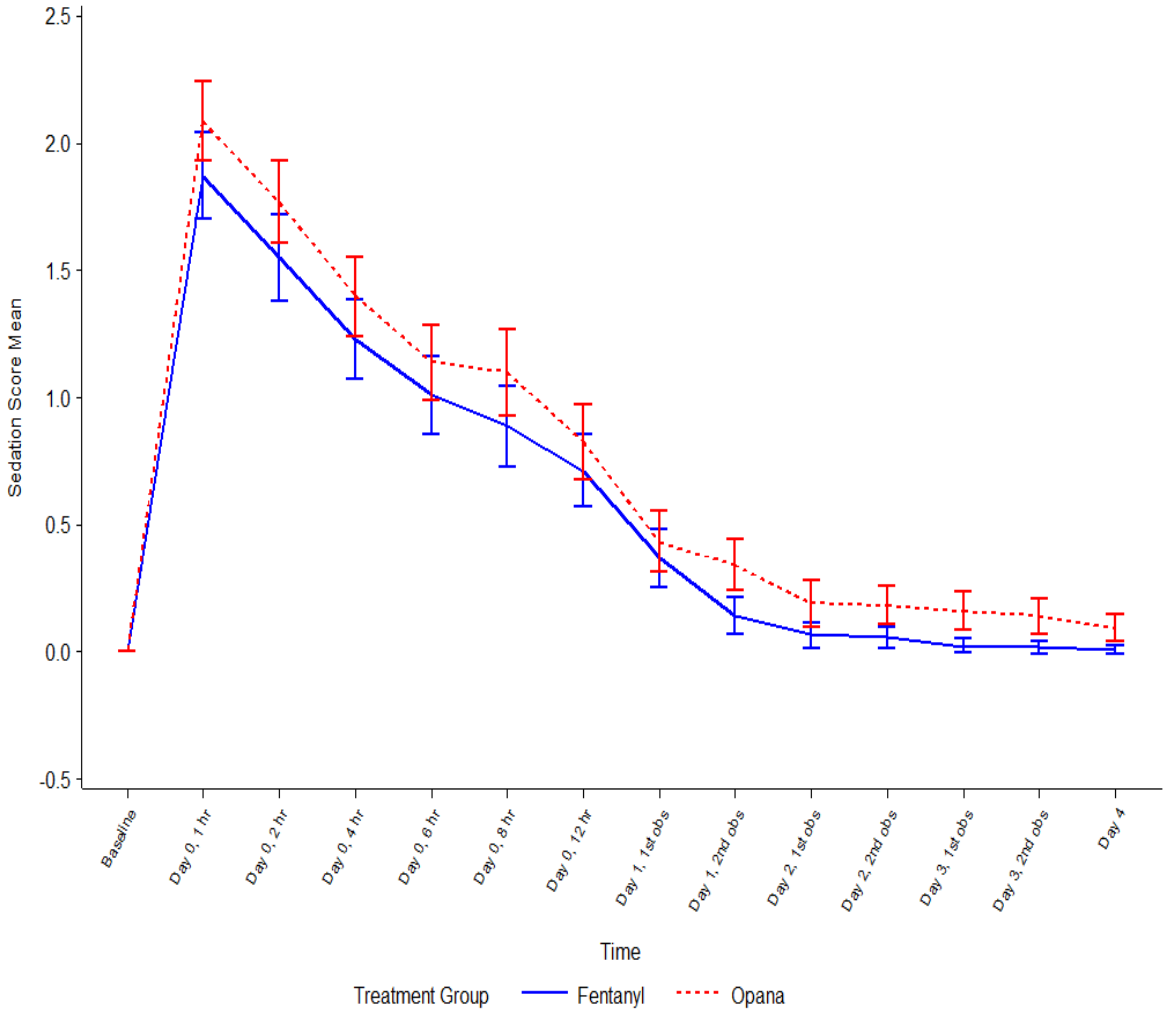
If the sedation score was $\geq$ 2, then the dog was considered to be too sedated to adequately assess analgesic effects, and the pain assessment at that time was not conducted.

9. Statistical Analysis: The primary variable was the dropout (failure) rate due to lack of pain control or opioid reversal. A non-inferiority evaluation was used to compare RECUVYRA with Oxymorphone with respect to dropout rate. The one-sided upper 95% confidence bound for the difference "RECUVYRA – Oxymorphone" was to be less than 15% for treatment with RECUVYRA to be considered non-inferior to treatment with oxymorphone.

c. Results:

Sedation: There was sedation observed in both treatment groups. At all time points, sedation score means were lower in RECUVYRA-treated dogs compared to those administered oxymorphone (Figure 2). On Day 0, the percentage of dogs which were too sedated for a pain assessment (sedation scores $\geq$ 2) ranged from 56% at 1 hour post-extubation to 14% at 12 hours post-extubation in RECUVYRA-treated dogs. For oxymorphone-treated dogs, the corresponding percents were 72% at 1 hour post-extubation and 19% at 12 hours post-extubation. On the first pain assessment of Day 1, 8% of oxymorphone- and 7% of RECUVYRA-treated dogs had sedation scores $\geq$ 2 and this decreased to 3% and 2% by the second assessment. By Day 2, 1-2 dogs in either group had sedation scores $\geq$ 2. No RECUVYRA-treated dogs had sedation scores $\geq$ 2 after the first assessment on Day 2 through the remainder of the study (through 96 hours post-extubation).

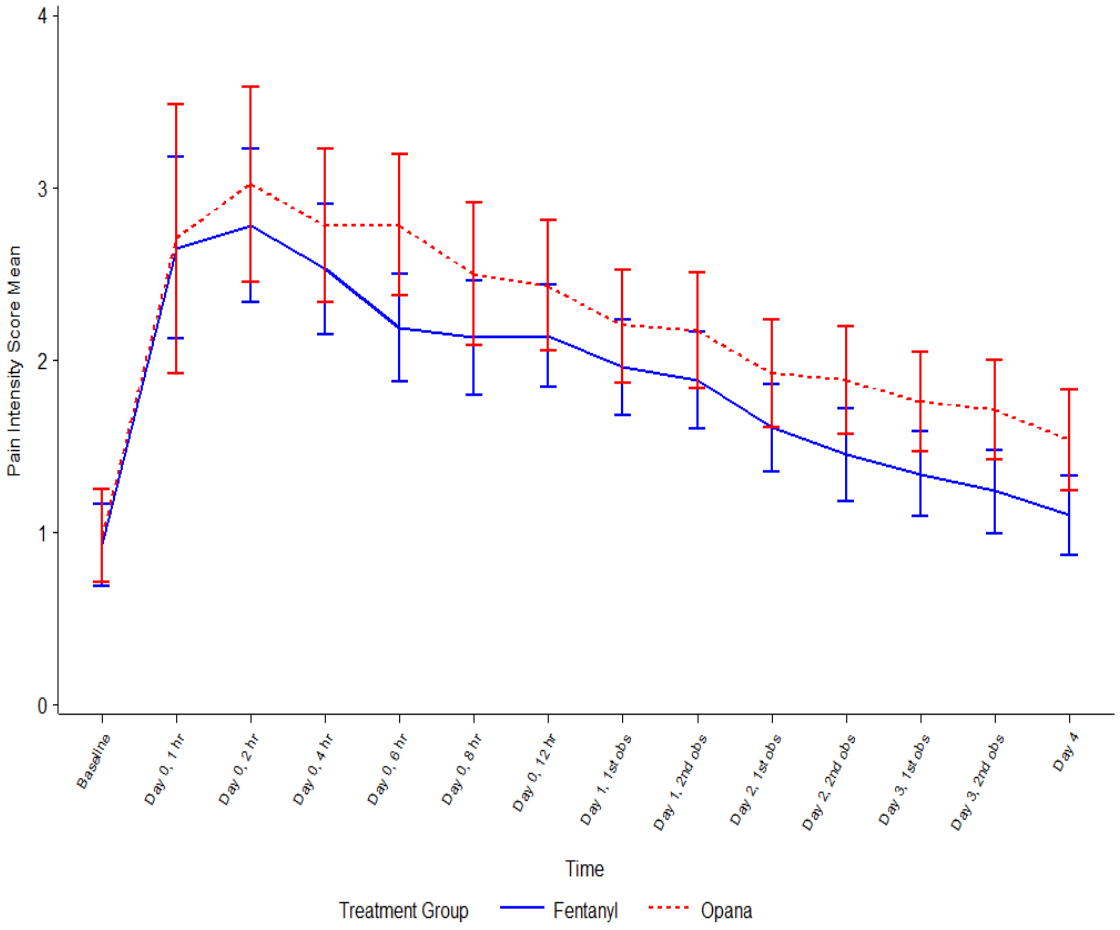
Figure 2: Mean sedation scores (±SEM) from pre-surgical (baseline) to 4 days following surgery. Possible scores were from 0 (no sedation) to 4 (unresponsive).



The length of the error bars is 2 standard errors from the means.

Pain: Dogs were assessed for pain using the modified Glasgow Composite Pain Scale (GCPS) by a trained observer with a total possible score of 20. Dogs with a score of ≥ 8 were considered treatment failures and administered a supplemental analgesic (Figure 3).

Figure 3: Mean pain scores (±SEM) from pre-surgical (baseline) to 4 days following surgery.



Excludes pain score(s) inadvertently recorded when sedation score > 1.
For dogs removed prior to completion of the study, all remaining pain scores were set to 8 (removal criteria) for periods not assessed.
The length of the error bars is 2 standard errors from the means.

A total of 9 dogs were considered treatment failures in this study; 2 dogs treated with RECUVYRA, and 7 dogs treated with oxymorphone. Of the two RECUVYRA treatment failures, both were removed due to lack of pain control. No RECUVYRA-treated dogs were removed from the study due to naloxone reversal. For oxymorphone treatment failures, 3 dogs were withdrawn due to lack of pain control, and 4 dogs were administered naloxone for opioid reversal due to adverse reactions. The 2 RECUVYRA treatment failures were both withdrawn 1 hour post-extubation with pain scores of 8 and 11. The 3 oxymorphone treatment failures were withdrawn on Day 0 at 6 and 12 hours post-extubation and Day 2 at the first assessment of the day, with scores of 8-10.

The dropout rate in the RECUVYRA treatment group was 1.61%, and the dropout rate in the oxymorphone treatment group was 5.56%. The one-sided upper 95% confidence bound was -1.0%, which is less than 15%. Therefore, based on dropout rate, RECUVYRA is non-inferior to oxymorphone.

d. Adverse Reactions:

Reported adverse reactions: Adverse reactions were reported in 13 RECUVYRA-treated dogs (10.5%) and 32 oxymorphone-treated dogs (25.2%). These adverse reactions are itemized by category as follows:

Table 4a: Adverse Reactions from field study by type of adverse reaction

Category	Fentanyl (N=124)		Oxymorphone (N=127)	
	n	%	n	%
Emesis	5	4.0	18	14.2
Hypothermia	1	0.8	12	9.4
Bradycardia	1	0.8	6	4.7
Diarrhea	0	0.0	5	3.9
Sedation	0	0.0	4	3.1
Anorexia	2	1.6	2	1.6
Bradypnea	0	0.0	2	1.6

Table 4b: Weight Loss[1]

	Fentanyl (N=123)		Oxymorphone (N=126)	
	n	%	n	%
Weight Loss (>0-5%)	68	55.3	62	49.2
Weight Loss (>5% - 10%)	34	27.6	48	38.1
Weight Loss (>10% - 15%)	2	1.6	10	7.9

[1]Percentages for weight loss were based on dogs with both a pre-dosing and termination body weight approximately 4 days following surgery.

Physiological adverse reactions during surgery:

Abnormal physiological effects monitored during surgery are summarized below:

Table 5: Abnormal Physiological Effects During Surgery

Category	Fentanyl (N=124)	Oxymorphone (N=127)
Tachypnea (>20 breaths/min)	75 (60.5%)	73 (57.5%)
Bradypnea (<10 breaths/min)	74 (59.7%)	70 (55.1%)
Hypertension[1]	26 (33.8%)	21 (25.9%)
Hypotension[1]	18 (23.4%)	33 (40.7%)
Hypothermia (<95°F)	18 (14.5%)	47 (37.0%)
Tachycardia (>180 beats/min)	11 (8.9%)	1 (0.8%)
Bradycardia (<50 beats/min)	6 (4.8%)	7 (5.5%)
Arrhythmia Noted[2]	2 (1.6%)	2 (1.6%)
Pyrexia (>102.5°F)	1 (0.8%)	1 (0.8%)
Reduced Pulse Oximetry (<85%)	0 (0.0%)	1 (0.8%)

[1]Combined results for all blood pressure measurements (mean arterial pressure, systolic pressure, or diastolic pressure). Normal BP values: 60-110 mmHg for mean arterial pressure, 110-160 mmHg for systolic pressure, 70-90 mmHg for diastolic pressure. Percentages were based on the 77 fentanyl dogs and 81 oxymorphone dogs with measured blood pressures.
[2]Fentanyl group: bradycardia/supraventricular tachycardia; Oxymorphone group: undesignated

Deaths: There were no deaths during the study; however 1 fentanyl-treated dog was euthanized without necropsy after developing central blindness approximately 1 month after study completion. Further diagnostics were not conducted.

e. Conclusion: Treatment with RECUVYRA at a dosage of 1.2 mg/lb (2.7 mg/kg) applied topically to the dorsal scapular area as a single application, 2 to 4 hours prior to orthopedic surgery, was safe and effective for controlling pain over 4 days following orthopedic procedures.

2. Type of Study: Field Study Postoperative Pain Evaluation of a Topical Fentanyl Solution following Soft Tissue Surgery in Dogs

a. Title: ARDG01-C-02: Clinical Study: Postoperative Pain Evaluation of a Topical Fentanyl Solution following Soft Tissue Surgery in Dogs

b. Investigators and Study Locations:

Table 6: Investigators and Study Locations

Richard N. Benjamin, DVM Berkley, CA	Scott Buzhardt, DVM Zachary, LA
Shane Daigle, DVM Cedar Park, TX	Peter Davis, DVM Augusta, ME
Samuel Geller, VMD Quakertown, PA	Mark Girone, DVM Antioch, TN
Kristy Lively, DVM Farragut, TN	Mark Marks, DVM Lawrence, KS
Andrew Pickering, DVM Terre Haute, IN	Wanda Pool, DVM Centreville, VA
Mike Shelton, DVM McKinney, TX	Roger L. Sifferman, DVM Springfield, MO
Joe Wurster, DVM Wichata Falls, TX	

c. Study Design: This was an active controlled, double-masked, multi-centered field study. The objective was to evaluate the clinical effectiveness and safety of RECUVYRA following soft tissue surgery in dogs.

1. Animal Details: Two hundred and fifty-one (251) client-owned animals were enrolled and received at least one treatment in this study. No more than 40% of all valid cases were provided from any one study site. Dogs were 6 months or older and weighed $\geq$ 6 pounds at the time of treatment. Both intact and castrated males and intact and ovariohysterectomized females were enrolled.

Animals enrolled in the study included 93 males and 158 females. Of these, 67 were intact males, 26 were castrated males, 116 were intact females, and 42 were spayed females, ranging in age from 0.5 – 13 years. Approximately 75% of the dogs were purebred. Approximately 37% of the total surgery types were ovariohysterectomy. The other types of surgery (and percent of cases) included: tumor removal (~16%),

cystotomy (~13%), liver lobectomy/biopsy (~12%), ear crop (~9%), enterotomy (~6%), lateral ear resection (~5%), and splenectomy (~2%).

2. Inclusion/Exclusion Criteria and Post-Inclusion Removal Criteria:
A dog was eligible for inclusion in the study if:
    a) it met the animal details criteria above
    b) it was presented for ovariohysterectomy, lateral ear resection, ear crops, or laparotomy that included one of the following procedures: cystotomy, enterotomy, splenectomy (partial or full), liver lobectomy or biopsy, kidney removal or biopsy, or tumor removal (including cryptorchid, retained testes).
    c) it had no clinically relevant medical abnormalities detected on hematology or serum chemistry, or physical examination (judged by the Investigator to conflict with the ability of the patient to undergo surgery, dosing or study response measurements)
    d) it had no history of seizures
    e) it had a score of P1 or P2 for the American Society of Anesthesiologists (ASA) system
    f) the Owner had been informed of risks and had given informed consent to include the dog in the study by signing the Owner Consent Form, and stated that the dog was current on immunizations as required by local and/or state authorities

    A dog was excluded from the study if it:
    a) had not met the inclusion criteria above
    b) exhibited an extremely fractious nature
    c) was pregnant, suspected to be pregnant (with the exception of females scheduled for ovariohysterectomy), or lactating; or was a male intended for breeding
    d) had received short-acting systemic corticosteroids within the last 14 days
    e) had received NSAIDs within 24 hours prior to surgery
    f) had received long-acting corticosteroids within the last 30 days
    g) had another orthopedic, neurological, or uncontrolled systemic disorder which required medical attention
    h) had had orthopedic surgery within the last 6 months
    i) had a known sensitivity to opioids, NSAIDs, or to any of the anesthetic articles to be used in the study

    Any dog removed from the study remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

3. Application Site Preparation: If the haircoat allowed direct contact of the applicator tips to the skin, no specific hair clipping or preparation was necessary. For double coated dogs such as Siberian Huskies, where the applicator tips could not directly deposit RECUVYRA onto the skin, clipping the application site was necessary. To maintain blinding, the decision and actual clipping of the application site was done at the time of the pre-

surgical physical examination without knowledge of the dog's eventual treatment group assignment.

4. Drug Administration: Dogs randomized to RECUVYRA received a single, dermal, topical application on the dorsal scapular area approximately 2 - 4 hours prior to surgery according to the following dosing table:

Table 7: Dosing in mL by body weight

Body Weight		
Lb	Kg	Dose (mL)
6.0 to 9.3	3.0 to 4.2	0.2
9.4 to 13.4	4.3 to 6.1	0.3
13.5 to 17.6	6.2 to 8.0	0.4
17.7 to 21.8	8.1 to 9.9	0.5
21.9 to 25.9	10.0 to 11.7	0.6
26.0 to 30.1	11.8 to 13.6	0.7
30.2 to 34.3	13.7 to 15.5	0.8
34.4 to 38.4	15.6 to 17.4	0.9
38.5 to 42.6	17.5 to 19.3	1.0
42.7 to 46.8	19.4 to 21.2	1.1
46.9 to 50.9	21.3 to 23.1	1.2
51.0 to 55.1	23.2 to 25.0	1.3
55.2 to 59.3	25.1 to 26.9	1.4
59.4 to 63.4	27.0 to 28.8	1.5
63.5 to 67.6	28.9 to 30.6	1.6
67.7 to 71.8	30.7 to 32.5	1.7
71.9 to 75.9	32.6 to 34.4	1.8
76.0 to 80.1	34.5 to 36.3	1.9
80.2 to 84.3	36.4 to 38.2	2.0
84.4 to 88.4	38.3 to 40.1	2.1
88.5 to 92.6	40.2 to 42.0	2.2
92.7 to 96.8	42.1 to 43.9	2.3
96.9 to 100.9	44.0 to 45.8	2.4
101.0 to 105.1	45.9 to 47.7	2.5
105.2 to 109.3	47.8 to 49.6	2.6
109.4 to 113.4	49.7 to 51.4	2.7
113.5 to 117.6	51.5 to 53.3	2.8
117.7 to 121.8	53.4 to 55.2	2.9
121.9 to 125.0	55.3 to 57.0	3.0

To prevent direct contact with human skin, latex or nitrile gloves, protective glasses, and a laboratory coat were worn when handling and/or applying the solution. The applicator tips were placed directly onto the skin in the dorsal scapular area, making sure that tips were in direct contact with the skin. Up to ½ mL was applied onto the skin without moving the applicator tip. The applicator tip was then re-positioned at least 1 inch from the initial site and up to ½ mL was applied. The

reposition and application steps were repeated until the entire volume was applied to the dog. The dog was restrained for approximately 2 minutes after application and no contact was made with the site for 5 minutes following application.

5. Active Control Veterinary Product: The active control product was oxymorphone hydrochloride. For dogs randomized to the control group, oxymorphone hydrochloride was administered subcutaneously in the dorsal scapular region 2 – 4 hours prior to surgery, at the time of extubation and every 6 hours through and including 90 hours (+ 1 hour) post-extubation. To maintain masking, dogs in the RECUVYRA group received a "mock dose" (physical handling of dogs similar to a subcutaneous injection without any treatment or injection) at the time of extubation and every 6 hours through and including 90 hours (+ 1 hour) post-extubation. The amount of the oxymorphone hydrochloride administered at each dosing period was determined from the table below.

Table 8: Oxymorphone Dosing Table

Body Weight (lbs)	Dosage (mLs)*
5 to 15	1.5
≥15 to 30	3.0
≥30 to 60	4.5
Over 60	6.0

*The dosing table reflects converted doses using an oxymorphone concentration of 1 mg/mL (OPANA). Doses are equivalent to the veterinary dosing table (NUMORPHAN) that is based on a 1.5 mg/mL concentration of oxymorphone.

6. Opioid Reversal: If at any time during the study a dog showed severe adverse effects consistent with opioid intoxication (such as non-responsive unconsciousness, seizure, marked abdominal breathing), an intravenous dose of naloxone hydrochloride (0.4 mg/mL solution at a dose level of 0.04 mg/kg) was administered. If clinical reversal was not observed after 2 to 3 minutes, administration of naloxone (at the same dose level) was repeated. Any dog requiring reversal with naloxone was considered a treatment failure for statistical analyses, but remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

7. Anesthesia: Anesthetic protocols were similar across all clinics in that dogs were anesthetized using a combination of the following agents according to the veterinarian's preference:

   Anesthetic Premedication:
   - i. glycopyrrolate
   - ii. acepromazine
   - iii. atropine
   - iv. midazolam
   - v. diazepam

   Anesthetic Induction:

i. propofol
ii. thiopental
iii. ketamine/diazepam
iv. tiletamine/zolazepam

Anesthetic Maintenance
i. nitrous oxide
ii. isoflurane
iii. sevoflurane

8. Measurements and Observations: A physical examination, including blood samples for serum chemistry and hematology was performed for all candidate dogs up to Day -1. A termination physical examination, including blood samples, was conducted on Day 4. For dogs allotted to the RECUVYRA group, a single blood sample for fentanyl assay was randomly collected from Day 0 through Day 4.

Dogs were assessed for pain using the modified Glasgow Composite Pain Scale (GCPS; see scoring system described above for orthopedic procedure field study) by a trained observer at the following time points: prior to treatment (up to Day -1 or on Day 0); Day 0 - approximately 1, 2,4, 6, 8, 12 hours post-extubation; Day 1 – approximately 24 hours post initial treatment then 6 – 8 hours later; Day 2 – approximately 48 hours post initial treatment then 6 – 8 hours later; Day 3 – approximately 72 hours post initial treatment then 6 – 8 hours later; and Day 4 – approximately 96 hours post initial treatment. Dogs with a score of ≥ 8 on the GCPS were administered a NSAID supplemental analgesic. Any dog requiring supplemental analgesia was considered a treatment failure for statistical analyses, but remained at the clinic until the scheduled study discharge on Day 4 for safety assessments per standard clinic practice.

Prior to pain assessments, each dog was assessed for sedation according to the following scale:

Sedation Score:
0 - No Sedation Present
1 - Slight Sedation - almost normal; able to stand easily, but appears somewhat fatigued, subdued or somnolent.
2 - Moderate Sedation - able to stand but prefers to be recumbent; sluggish; ataxic or uncoordinated.
3 - Profound Sedation - unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency.
4 - Unresponsive - in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

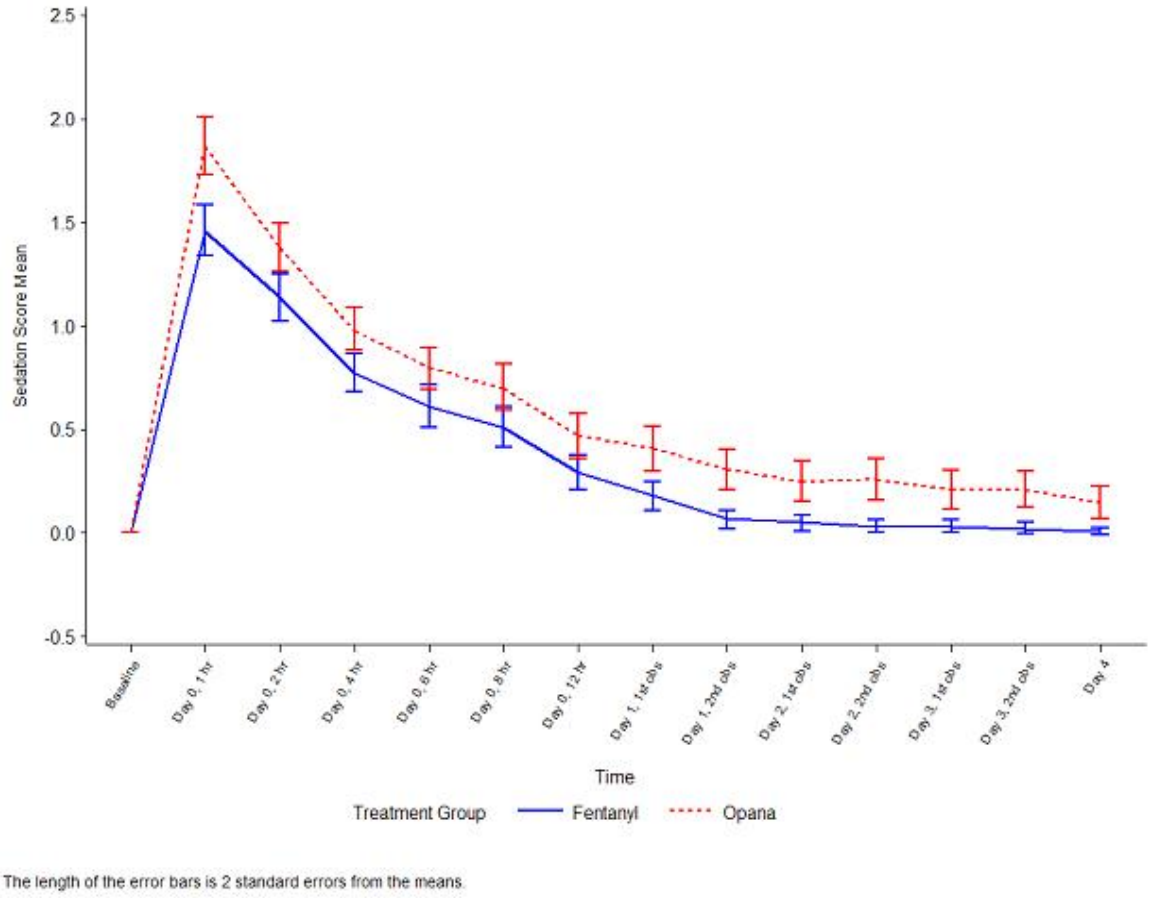
If the sedation score was > 2, then the dog was considered to be too sedated to adequately assess analgesic effects, and the pain assessment at that time was not conducted.

9. Statistical Analysis: The primary variable was the dropout (failure) rate due to lack of pain control or opioid reversal. A non-inferiority evaluation was used to compare RECUVYRA with Oxymorphone with respect to dropout rate. The one-sided upper 95% confidence bound for the difference "RECUVYRA – Oxymorphone" was to be less than 15% for treatment with RECUVYRA to be considered non-inferior to treatment with oxymorphone.

d. Results:

Sedation: There was sedation observed in both treatment groups. At all time points, sedation score means were lower in RECUVYRA-treated dogs compared to those administered oxymorphone (Figure 4). On Day 0, the percentage of dogs that were too sedated for a pain assessment (sedation scores $\geq$ 2) ranged from 42% at 1 hour post-extubation to 0.8% at 12 hours post-extubation in RECUVYRA-treated dogs. For oxymorphone-treated dogs, the corresponding percents were 69% at 1 hour post-extubation and 3% at 12 hours post-extubation. A small percentage of oxymorphone-treated dogs continued to be at least moderately sedated throughout the entire study. In contrast, no RECUVYRA-treated dogs had sedation scores $\geq$ 2 after the 12 hour post-extubation assessment on Day 0 through the remainder of the study (through 96 hours post-extubation).

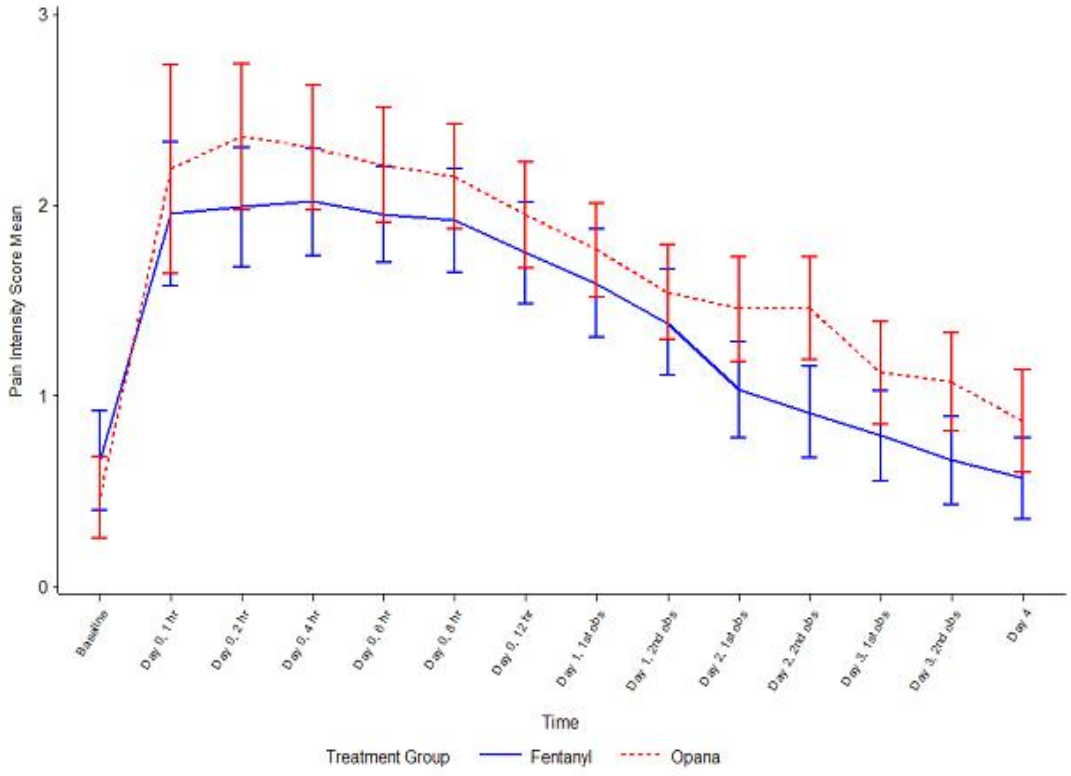
Figure 4: Mean sedation scores (±SEM) from pre-surgical (baseline) to 4 days following surgery. Possible scores were from 0 (no sedation) to 4 (unresponsive).



The length of the error bars is 2 standard errors from the means.

Pain: Dogs were assessed for pain using the modified Glasgow Composite Pain Scale (GCPS) by a trained observer with a total possible score of 20. Dogs with a score of ≥ 8 were considered treatment failures and administered a supplemental analgesic (Figure 5).

Figure 5: Mean pain scores (±SEM) from pre-surgical (baseline) to 4 days following surgery. All



Excludes pain score(s) inadvertently recorded when sedation score > 1.
For dogs removed prior to completion of the study, all remaining pain scores were set to 8 (removal criteria) for periods not assessed.
The length of the error bars is 2 standard errors from the means.

A total of 12 dogs were considered treatment failures in this study; 2 dogs treated with RECUVYRA and 10 dogs treated with oxymorphone. Of the 2 RECUVYRA treatment failures, both were removed due to lack of pain control. No RECUVYRA-treated dogs were removed from the study due to naloxone reversal. For oxymorphone-treated treatment failures, 5 dogs were withdrawn due to lack of pain control, and 5 dogs were administered naloxone for opioid reversal due to adverse reactions. The 2 RECUVYRA treatment failures were withdrawn 1 hour and 6 hours post-extubation with pain scores of 8 and 10. Of the 5 oxymorphone treatment failures, 2 were withdrawn on Day 0 at 2 or 4 hours post-extubation, and the other 3 were withdrawn on Day 1 or 2, with pain scores of 8-15.

The dropout rate in the RECUVYRA treatment group was 1.60%, and the dropout rate in the oxymorphone treated dogs was 8.00%. The one-sided upper 95% confidence bound was -3.1%, which is less than 15%. Therefore, based on dropout rate, RECUVYRA is non-inferior to oxymorphone.

e. Adverse Reactions:

Reported adverse reactions: Adverse reactions were reported in 31 RECUVYRA -treated dogs (24.8%) and 52 oxymorphone-treated dogs (41.3%). These adverse reactions are itemized by category as follows in Table 9a and Table 9b:

Table 9a: Adverse Reactions in field study by type of adverse reaction

Category	Fentanyl (N=125)		Oxymorphone (N=126)	
	n	%	n	%
Emesis	4	3.2	30	23.8
Hypothermia	13	10.4	28	22.2
Sedation	0	0.0	10	7.9
Diarrhea	9	7.2	9	7.1
Anorexia	1	0.8	6	4.8
Hypersalivation	1	0.8	5	4.0
Tachypnea	0	0.0	4	3.2
Anxiety/Restlessness	0	0.0	3	2.4
Dehydration	1	0.8	3	2.4
Bradycardia	0	0.0	2	1.6
Incision Site Infection	0	0.0	2	1.6
Death	1	0.8	1	0.8

Table 9b: Weight Loss[1]

	Fentanyl (N=124)		Oxymorphone (N=123)	
	n	%	n	%
Weight Loss (>0-5%)	59	47.6	49	39.8
Weight Loss (>5% - 10%)	20	16.1	38	30.9
Weight Loss (>10% - 15%)	2	1.6	10	8.1
Weight Loss (>15%)	2	1.6	1	0.8

[1]Percentages for weight loss were based on dogs with both a pre-dosing and termination body weight approximately 4 days following surgery.

Physiological adverse reactions during surgery:

Abnormal physiological effects monitored during surgery are summarized below in Table 10:

Table 10: Abnormal Physiological Effects Monitored during Surgery

Category	Fentanyl (N=125)	Oxymorphone (N=125)
Tachypnea (>20 breaths/min)	83 (66.4%)	78 (62.4%)
Hypotension[1]	14 (45.2%)	13 (44.8%)
Hypertension[1]	11 (35.5%)	11 (37.9%)
Bradypnea (<10 breaths/min)	42 (33.6%)	38 (30.4%)
Tachycardia (>180 beats/min)	15 (12.0%)	7 (5.6%)
Hypothermia (<95°F)	5 (4.0%)	24 (19.2%)
Bradycardia (<50 beats/min)	3 (2.4%)	0 (0.0%)
Pyrexia (>102.5°F)	2 (1.6%)	0 (0.0%)

[1]Combined results for all blood pressure measures (mean arterial pressure, systolic pressure, or diastolic pressure). Normal values: 60-110 mmHg for mean arterial pressure, 110-160 mmHg for systolic pressure, 70-90 mmHg for diastolic pressure. Percentages were based on the 31 fentanyl dogs and 29 oxymorphone dogs with measured arterial blood pressures.

Deaths: There were two deaths (one in each treatment group) during the course of the study. The death of the oxymorphone-treated dog was the result of pulmonary embolism and stroke. The cause of death of the fentanyl-treated dog was bacterial pneumonia caused by chronic vomiting and secondary aspiration, likely present prior to surgery.

f. Conclusion: Treatment with RECUVYRA at a dosage of 1.2 mg/lb (2.7 mg/kg) applied topically to the dorsal scapular area as a single application, 2 to 4 hours prior to soft tissue surgery was safe and effective for controlling pain from soft tissue procedures over 4 days.

III. TARGET ANIMAL SAFETY:

A. Title: ARDG01-C-03 (Ricerca Study No. 021885): Evaluation of the Margin of Safety of a Topical Fentanyl Solution in Mongrel Dogs

1. Type of Study: Non-Clinical Laboratory Study (conducted under GLP)

2. Investigator: Michael C. Savides, Ph.D.
Ricerca Biosciences LLC
Concord, OH 44077

3. General Design

a. Purpose of Study: To evaluate the margin of safety of RECUVYRA when administered to healthy adult mongrel dogs (eight dogs per group) at 0, 2.6, 5.2, and 7.8 mg/kg (0, 1, 2, and 3 times the dose) as a topical application administered every 4 days for a total of 3 doses.

b. Description of Test Animals: Thirty-two purpose bred laboratory mongrel dogs 1-2 years of age (16 male, 16 female), 8 dogs per dose group.

c. Fentanyl: Final market formulation of RECUVYRA (fentanyl solution at 50 mg/mL).

d. Control and Treatment Groups:

Table 11: Treatment groups, dosage, dose volume, number, and gender

Tx Group	Dosage (mg/kg)	Dose Vol (mL/kg)	Number and Sex of Dogs
1	0 (0X)	0.156	4M, 4F
2	2.6 (1X)	0.052	4M, 4F
3	5.2 (2X)	0.104	4M, 4F
4	7.8 (3X)	0.156	4M, 4F

e. Randomization: Dogs were randomized in a manner that resulted in similar body weights between groups, with 4 males and 4 females in each of the 4 test groups. Animals were initially segregated by gender, then ranked by descending body weight. Animals were assigned to treatment groups in blocks of 4, with each treatment group appearing once within each block, thus balancing the weights across the treatment groups. Animals were randomized to single cages, such that it was not possible for the Study Director or any person involved in animal observations to determine the treatment group.

f. Drug administration: Dogs in each group were dosed at 0, 2.6, 5.2, and 7.8 mg/kg every 4 days for a total of 3 doses. Dogs in the control group received saline at a volume equivalent to the 3X dose. Dogs were weighed on the days of dosing (days 0, 4, and 8).

g. Route of administration: Topical. The dose was applied from a syringe to a clipped area on the ventral abdomen in a serpentine manner. The dog was then restrained for approximately 2 minutes or until the solution was observed to have dried. [Note that for bioavailability reasons, the approved application site is the dorsal scapula area.]

h. Study duration: Twelve days.

i. Variables measured: General health observations, clinical observations, physical examination, ophthalmic examination, electrocardiograms (ECG), body weight, food consumption, fecal examination, hematology, serum chemistry, urinalysis, plasma fentanyl concentration, and necropsy following euthanasia (including gross and histopathology examinations).

j. Statistical methods: For the continuous variables measured at more than one time point, a repeated measures analysis of covariance model was performed to test the effects of dose group, sex, time and all the two and three-way interactions. Baseline measurements were included in the model as covariates. For continuous variables measured once an analysis of variance model was performed to test the effects of dose group, sex and the two-way interaction. Follow-up pairwise mean comparisons between the 0X and each non-zero dose groups were performed, as necessary, using linear contrasts with significance level 0.10.

4. Results

Three dogs died as a result of transdermal fentanyl administration. Death was due to endotoxic shock produced by severe gastrointestinal stasis complicated by continued hypothermia and sedation. All deaths occurred between the second and third doses. Two dogs (2X group) died on days 4 and 7, and the third dog (3X group) died on day 5. During the first dose period, these dogs had mostly moderate to profound sedation. One 2X dog was unresponsive 4 hours after the first dose and profoundly sedated at the next observation (12 hours). All 3 dogs had severe hypothermia (body temperature < 98° F), with the lowest temperatures ranging from 90.9-93.2° F. The three dogs had bradycardia (heart rate < 60 beats per minute) and decreased respiratory rates. Lowest heart and respiratory rates ranged from 32-40 beats per minute and 12-16 breaths per minute, respectively. Food consumption was near zero. Two of the dogs lost 7% of their body weight, and the third lost 11% body weight between doses 1 and 2. Clinical observations included mydriasis and salivation in 2 of the dogs, corneal opacity in 1 dog, soiled coat in 1 dog, cold to the touch in 1 dog, and vomiting in 1 dog. The 3 dogs also had lack of feces, and 2 of the dogs each had a single observation of blood in the feces on days 3 or 4.

All 3 dogs were still hypothermic at the time of the second dose application, with temperatures ranging from 94.5-97.2° F. Clinical pathology results (shown in Table 1 below) were available in only 2 dogs on day 4, as an insufficient sample was obtained from the third dog (2X). Both dogs were severely dehydrated, having increased hematocrit (HCT), hemoglobin (HGB), albumin (ALB), globulin (GLOB), and total protein (TP) values (all above the normal range). Both dogs also had APTT, fibrinogen (FIB), and PT values above the normal range. Platelet counts were normal. An additional blood sample for hematology was obtained on day 5 prior to the death of the 3X group dog.

Table 12: Clinical Pathology Results in Two Dogs with Unexpected Deaths

Dog	Study Day	ALB (2.63-3.57 g/dL)	GLOB (2.11-3.11 g/dL)	TP (5.00-6.50 g/dL)	APTT (9.93-17.07 sec.)	FIB (158.3-340.7 mg/dL)	PT (5.90-8.70 sec.)	HCT (35.4-50.7%)	HGB (11.8 – 17.2 g/dL)	WBC (4.9-15.1 K/µL)
2X	0	3.1	3.6	6.7	14.1	270	8.4	45.9	16.1	6.7
	4	4.3	5.1	9.4	18.3	650	9.7	69.5	23.5	10.41
3X	0	3.5	3.3	6.8	15.3	165	8.9	48.7	17.4	6.86
	4	3.8	4	7.8	18.5	660	9.6	64.3	22.0	8.71
	5							80.5	26.9	12.87

Bolded values are above the normal reference ranges shown at top of table

Gross findings on necropsy of the 3 dogs included red discoloration of the intestines and other organs, and dark red or black intestinal contents in 2 of the 3 dogs. One 2X dog had multifocal ulceration in the small intestine and colon, and the second 2X dog had multifocal erosions in the small intestine and colon, although these observations were identified as likely post-mortem changes by the examining pathologist. Histopathological examination showed diffuse, moderate, villous and mucosal congestion of the intestines (2X and 3X dog); multifocal, moderate epithelial necrosis in the small intestine (2X dog with multifocal erosions); and diffuse, sinusoidal congestion in the liver (2X and 3X dog). All 3 dogs had bilateral, diffuse, moderate to marked proteinaceous casts in the renal tubules.

Severe adverse reactions (besides death) were observed in other dogs. In particular, 1 dog in the 1X group and 1 dog in the 2X group had the greatest decreases in temperature (88.9° and 84.2° F), heart rate (28 and 16 beats per minute) , and respiratory rate (8 and 4 breaths/minute), and the highest level of sedation (profound in both dogs) in their respective groups. These dogs also tended to have the most abnormal clinical pathology variables, and both had blood in the feces, as well as mucosal congestion of the colon on histopathology examination. The 1X dog had red discoloration of the colon and the 2X dog had dark red colon contents on gross necropsy.

a. General Health and Clinical Observations: There were abnormal observations in both the treated and untreated groups. The 1X dogs had salivation, vomiting, and dilated pupils. There were more abnormal observations in the 2X and 3X groups, mostly related to the sedative and hypothermic effects of fentanyl. These findings included corneal opacity, labored breathing and red urination in the 2X group; tremors in the 3X group; and soiled coat, thin, cold to the touch, ataxia, and eye discharge in both the 2X and 3X groups. Transient erythema was noted at the drug application site in 2 dogs in the 1X group and 3 dogs in the 3X group within 1-4 hours after the first dose. One 1X dog had transient edema where the drug was applied after the second dose.

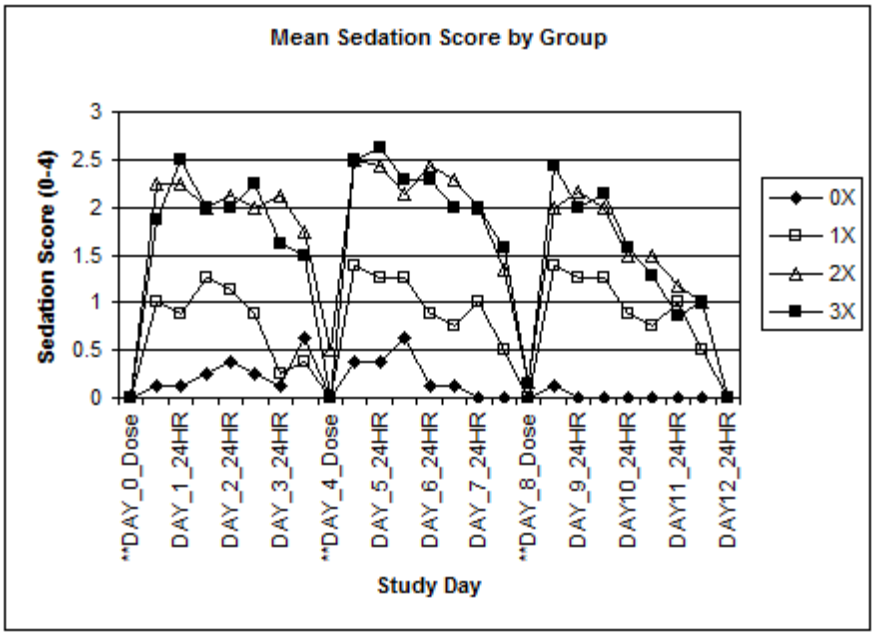
   Dogs in the treated groups had more fecal abnormalities, including blood in the feces, diarrhea, and lack of feces. Blood in the feces increased in severity with increased dose and repeated doses. Only 1 dog in the 0X group had blood in the feces, whereas 3 dogs in the 1X group, 5 dogs in the

2X group, and 4 dogs in the 3X group had blood in the feces. In the 1X group, one dog each had a single observation of blood in the feces after either the first or second dose; a third 1X dog had 4 observations after the second dose and 10 observations after the third dose.

Sedation was observed in all 4 groups after fentanyl dosing, with the 2X and 3X groups having the highest sedation scores. There were dogs in the 0X group with positive plasma fentanyl levels, therefore, observed sedation may have been due to drug effects in that group. There was large variability in the level of sedation, which ranged between slight to profound within all 3 treated groups. Sedation scores were highest during the second dose period.

Sedation was observed in individual dogs within 12 hours of the first dose of RECUVYRA in the 1X group, and as early as 1-4 hours in the higher dose groups. Sedation occurred more quickly after the second and third doses. In the 1X group, 3 dogs had slight or no sedation and 5 dogs had moderate sedation, 2 of which had additional observations of profound sedation. Most dogs in the 2X and 3X groups remained moderately to profoundly sedated. Mean sedation scores are shown in Figure 6 below.

Figure 6: Mean Sedation Scores over 3 Dose Periods



Sedation scores: 0=no sedation, 1=slight, 2=moderate, 3=profound
Asterisks designates dosing days

By the third dose period, dogs began to have lower sedation scores (Table 13 below), which suggested tolerance to the sedative effects of fentanyl.

Table 13: Number of Dogs with Sedation Scores ≥ 2 by Dose Period

Study Group	Number of Dogs (%) with Sedation Scores ≥ 2		
	Dose Period 1	Dose Period 2	Dose Period 3
0X	0 (0%)	2 (25%)	0 (0%)
1X	5 (62.5%)	4 (50%)	1 (12.5%)
2X	7 (87.5%)	7 (87.5%)	4 (66.67%)*
3X	8 (100%)	8 (100%)	6 (85.7%)*

*denotes % of 6 dogs remaining in 2X group, 7 dogs remaining in 3X group

b. Physical Examinations: Mean body temperatures, heart rates, and respiratory rates decreased in the treated groups after dosing. The largest decreases occurred in the 2X and 3X groups. Temperatures, heart rates, and respiratory rates continued to decrease as sedation scores increased during the 24 hour post-dosing period. Body temperatures and heart rates appeared to be less affected by successive dosing, whereas respiratory rates had a downward trend with each subsequent dose.

Body Temperature: The largest drop in mean body temperatures occurred about 12-24 hours after dosing. In the 1X group, individual dogs became hypothermic within 12 hours after the first dose. In all treated groups, hypothermia developed in some dogs by 4 hours following the second and third doses. Severe hypothermia was observed in all treated groups, with individual temperature measurements as low as 88.9, 84.2, and 92.1° F in the 1X, 2X, and 3X groups, respectively (Table 14 below).

At the time of the second dose, hypothermia was still present in the 1X group (1 dog), 2X group (4 dogs), and the 3X group (5 dogs). At the time of the third dose, only 2 dogs in the 3X group remained hypothermic, which suggested tolerance to the hypothermic effects of fentanyl.

Table 14: Dogs with Hypothermia (Body Temperature < 98° F)

Group	Dose Period 1 (Day 0-3)		Dose Period 2 (Day 4-7)		Dose Period 3 (Day 8-12)	
	no. of dogs below 98°F	body temp range °F	no. of dogs below 98°F	body temp range °F	no. of dogs below 98°F	body temp range °F
0X	1/8	97.0-101.5	3/8	93.7-102.0	1/8	97.7-102.0
1X	6/8	88.9-102.0	7/8	93.7-102.7	2/8	95.0-102.7
2X	8/8	84.2-101.1	8/8	89.6-102.2	5/6	92.1-101.7
3X	8/8	92.3-101.1	8/8	92.1-101.3	7/7	94.1-101.2

Heart Rate: Heart rates in individual dogs began declining within 4 hours after dosing, and reached the lowest mean levels 36 hours after the first dose, and about 12 hours after the second and third doses.

Bradycardia occurred in most treated dogs, and lasted about 2-3 days. Individual dogs in the 1X, 2X, and 3X groups had heart rate values as low as 28, 16, and 28 beats per minute respectively. After the third dose, there were fewer observations of bradycardia and the heart rate ranges were higher, which suggested tolerance to the bradycardic effects of fentanyl (Table 15 below).

Table 15: Dogs with Bradycardia (Heart Rate < 60 beats/ minute)

Group	Dose Period 1 (Day 0-3)		Dose Period 2 (Day 4-7)		Dose Period 3 (Day 8-12)	
	no. of dogs HR<60	HR range	no. of dogs HR<60	HR range	no. of dogs HR<60	HR range
0X	6/8	40-124	3/8	44-180	6/8	48-116
1X	7/8	32-108	7/8	28-112	6/8	48-140
2X	8/8	16-100	8/8	28-152	4/6	40-164
3X	8/8	28-104	8/8	40-120	6/6*	44-168

*Heart rate not measured for 1 dog during Dose Period 3.

Respiratory Rate: The lowest mean respiratory rates for all 3 treated groups occurred following the third fentanyl dose. Rates began dropping within 4 hours of fentanyl dosing, particularly in the 2X and 3X groups. In general, most 1X group dogs maintained minimum respiratory rates of 12-16 breaths per minute or higher after dosing. Individual dogs in the 1X group (2 dogs) had rates as low as 8 breaths per minute, and dogs in the 2X and 3X groups had rates as low as 4 breaths per minute following each dose of fentanyl (Table 16 below).

Table 16: Dogs with Bradypnea (Respiratory Rate < 10 breaths/minute)

Group	Dose Period 1 (Day 0-3)		Dose Period 2 (Day 4-7)		Dose Period 3 (Day 8-12)	
	no. of dogs RR<10	RR range	no. of dogs RR<10	RR range	no. of dogs RR<10	RR range
0X	0/8	16-44	0/8	16-40	0/8	16-32
1X	1/8	8-40	1/8	8-40	1/8	8-32
2X	2/8	4-36	3/8	4-36	3/6	4-28
3X	2/8	4-36	4/8	4-48	5/7	4-64

c. Ophthalmic Examinations: There were no treatment-related findings.

d. Electrocardiograms (ECGs): ECGs were obtained prior to dosing, and 1, 4, and 12 hours after dosing. A board-certified veterinary cardiologist reviewed the ECG results. Findings in some treated dogs included bradycardia, increases in PR and QT intervals (Table 17a and Table 17b), and the rhythm abnormalities shown in (Table 18) below. All of these changes were attributed to the autonomic effects of fentanyl.

Table 17a: Dogs with Increases in PR Intervals (normal range: 60-130 ms)

Group	Dose Period 1 (Day 0)		Dose Period 2 (Day 4)		Dose Period 3 (Day 8)	
	no. of dogs PR>130	PR range	no. of dogs PR>130	PR range	no. of dogs PR>130	PR range
0X	1/8	84-141	1/8	84-142	0/8	85-128
1X	0/8	93-124	1/8	81-151	0/8	86-127
2X	4/8	86-159	0/8	63-119	1/6	81-132
3X	1/8	78-132	0/8	77-114	0/6*	86-118

*Heart rate and ECGs not measured for 1 dog during Dose Period 3.

Table 17b: Dogs with Increases in QT Intervals (normal range: 150-250 ms)

Group	Dose Period 1 (Day 0)		Dose Period 2 (Day 4)		Dose Period 3 (Day 8)	
	no. of dogs QT>250	QT range	no. of dogs QT>250	QT range	no. of dogs QT>250	QT range
0X	0/8	190-246	0/8	180-244	0/8	171-231
1X	4/8	166-294	3/8	186-279	1/8	172-263
2X	6/8	187-328	3/8	170-321	4/6	199-300
3X	6/8	185-298	4/8	191-288	1/6*	193-282

*Heart rate and ECGs not measured for 1 dog during Dose Period 3.

Table 18: Cardiac Rhythm Abnormalities in Study Dogs

Group	Abnormal Rhythm	Study Time
2X	-2° atrioventricular (AV) block	Day 8: pre-dose, 1 hr, 12 hr
2X	-junctional escape complex -isorhythmic AV dissociation	Day 0: 12 hr Day 0: 12 hrs
3X	-idiojunctional rhythm	Day 4: pre-dose

e. Body Weight: Body weights decreased over the course of the study, with the greatest weight loss occurring in the 2X and 3X groups. Dogs lost the most weight in the first dose period. By the end of the study, 3 dogs in the 1X group lost 19-20% body weight, and three 1X dogs lost 5-10% body weight compared to day 0. The degree of weight loss was not always correlated with level of sedation, since 1 dog in the 0X group that lost 13% body weight and 1 dog in the 1X group that lost 20% body weight had almost no sedation over the course of the study. All dogs in the 2X and 3X groups lost between 10-21% body weight by day 12 (Table 19 below).

Table 19: Number of Dogs and % Body Weight Loss over 12 Days

Body Weight Loss	Dose Group			
	0X	1X	2X	3X
	No. of dogs	No. of dogs	No. of dogs	No. of dogs
0-5%	7	2	0	0
>5-10%	0	3	0	0
>10-15 %	1	0	2	4
> 15-21%	0	3	4	3
Total	8	8	6	7

f. Food Consumption: Daily food consumption decreased substantially after fentanyl dosing, especially in the higher dose groups. Consumption declined to nearly zero from day 1 to day 6 in the 2X and 3X groups. Following the third dose, declines in food consumption were less pronounced in all the treated groups. In the 1X group, food consumption decreased 87% after the first dose, then 70% and 37% after the second and third dose. Dogs in the 1X group returned to pre-treatment food consumption by the end of the study, whereas the 2X and 3X dogs reached approximately 45% of their day 0 consumption by day 12.

g. Clinical Pathology (Blood samples were taken on days 0, 4, 8, and 12)

1) Hematology:

Hematocrit (HCT), hemoglobin (HGB), and red blood cell (RBC) counts showed a treatment-related increase consistent with dehydration. The largest increase occurred on day 4, and values were lower after each subsequent dose. The 3X group had the highest mean values, which were above the normal range on all sample days after the first dose. Mean values for the 2X group were above normal on days 4 and 8, and

all 1X mean values remained within the normal range. In the 1X group, 3 of 8 dogs had HGB and RBC values above normal after the first dose, and 1 of these dogs also had a HCT value above the normal range. After the second dose, 2 of the 3 dogs had HGB, RBC, and HCT values above normal. By the third dose, only 1 of the 3 dogs had abnormal HGB, RBC, and HCT values, and this dog had a pre-existing elevated HGB on Day 0.

Some individual 2X and 3X dogs had an increase in reticulocytes on day 4, followed by a sharp decline on day 8 by as much as 90% from Day 4. By the end of the study, values in 2X group dogs had decreased an average of 81% from pretreatment levels, and 70% on average in the 3X group dogs. In the 1X group, 5 of 8 dogs had reticulocyte count decreases ranging from 18-85% on day 12 compared to day 0 values, whereas the other 3 dogs had reticulocyte increases by day 12.

Three dogs in the 3X group had white blood cell counts (WBC) and neutrophil counts above the normal range during the study. Each of the 3 dogs had one elevated value on either Day 4, 8, or 12, ranging from 15.98 and 17.97 K/µL (normal reference range 4.90-15.10 K/µL).

2) Serum Chemistry:

Treated dogs had higher albumin, globulin, and total protein values on day 4 than on day 0. These increases were most likely due to dehydration, and the mean values for the 2X and 3X groups were above the normal range. By day 12, mean values for the treated groups dropped below day 0 values, suggestive of protein loss. Two dogs each in the 2X and 3X groups had albumin values below the normal range by the end of the study.

3) Coagulation:

Two of the dogs that died (one 2X and the 3X dog) had sharp increases in APTT values on day 4 that were above the normal range. In addition to the dogs that died, one 2X dog had APTT values above the normal range on days 4, 8, and 12, and one 3X dog had a value above normal on day 8, which normalized on day 12.

There was a dose-related increase in mean fibrinogen values in all the treated groups. The maximal increase occurred on day 4, when 3 dogs in the 1X group, 5 dogs in the 2X group, and 8 dogs in the 3X group had values above the normal range. Most individual values decreased thereafter, but 1 dog in the 1X group, though normal previously, as well as 4 dogs in the 2X group and 3 dogs in the 3X group still had fibrinogen values above normal by the end of the study.

h. Pathology:

1) Necropsy: Table 20 below summarizes salient gross findings for the dogs euthanized at the conclusion of the study. Intestinal findings common to those seen in some of the dogs that died unexpectedly were red discoloration and dark red contents.

Table 20: Gross Findings from Scheduled Necropsy (Number of Dogs)

Observation	Group and Dose (mg/kg)			
	0 (0X)	2.6 (1X)	5.2 (2X)	7.8 (3X)
Bone marrow (femur) - pale/white	1	1	2	2
Heart - thickened AV valve		1	1	2
Intestine (colon) - red discoloration		1		1
Intestine (colon) - red streaking			1	
Intestine (colon) - dark red contents			1	
Intestine (duodenum) - red area				1
Kidney – bilateral cyst		1		1
Lung - tan area(s)		2	3	
Lung - red area(s)				2
Lung - firm area(s)				1
Thymus - small		2	5	6

2) Histopathology: Table 21 below summarizes findings for the dogs euthanized at the conclusion of the study. Important findings common to those seen in some of the dogs that died unexpectedly were mucosal congestion of the intestine (seen in 1-2 dogs in all treated groups) and proteinaceous casts in the renal tubules (one 1X dog).

Table 21: Histopathologic Findings from Scheduled Necropsy (Number of Dogs)

Observation	Group and Dose (mg/kg)			
	0 (0X)	2.6 (1X)	5.2 (2X)	7.8 (3X)
Epididymides - aspermia, bilateral, diffuse, marked			2	
Heart - inflammation, chronic active, right atrium: focal or locally extensive			1	1
Intestine (colon) - congestion, mucosa		1	2	1
Intestine (duodenum) - dilation, crypt				2
Intestine (jejunum) - dilation, crypt				1
Kidney - cast, proteinaceous, tubule, bilateral, diffuse, mild		1		
Lung - inflammation, fibrinopurulent, bronchiole, alveolus				3
Testes - degeneration, spermatogenic, seminiferous tubule, bilateral, diffuse	1		3	

3) Bone Marrow Evaluation: Results showed changes suggestive of an increased demand for white blood cells. The treated dogs had higher total myeloid cell counts, and lower total erythroid cell counts than the 0X dogs. The 2X and 3X groups were most affected and had similar values. Four dogs in the 1X group had increased myeloid to erythroid (M:E) ratios, ranging from 5.1:1 to 16.2:1 (normal reference range 0.75:1 to 2.5:1)[1]. All dogs in the 2X and 3X groups had increased M:E ratios, ranging from 3.9:1 to 17.6:1 in the 2X group, and 3.3:1 to 15:1 in the 3X group. In the 2X and 3X groups, dogs with the highest M:E ratios following necropsy generally had the highest peripheral WBC counts in their respective groups during the study.

i. Plasma Fentanyl Concentrations: Plasma fentanyl concentrations doubled from the first to the third dosing interval. Fentanyl concentrations appeared to show accumulation with successive doses in all treated groups.

5. Conclusion: Administration of topical RECUVYRA every 4 days at 2.6, 5.2, and 7.8 mg/kg (1X, 2X, and 3X the clinical dose) for 3 doses showed a narrow margin of safety. Two 2X dogs and one 3X dog died between the second and third dose due to endotoxic shock as a result of severe gastrointestinal stasis complicated by continued hypothermia and sedation. RECUVYRA caused variable levels of sedation that were sometimes profound, severe hypothermia, bradycardia, respiratory depression, dehydration, weight loss, decreased food consumption, blood in the feces, lack of feces, diarrhea,

[1] Willard MD, Tvedten H. The complete blood count and bone marrow examination: General comments and selected techniques. In: *Small Animal Clinical Diagnosis by Laboratory Methods, 4th edition.* St Louis: Saunders, 2004; 36.

vomiting, salivation, dilated pupils, decreased reticulocyte cell counts, increased coagulation variables, and increased myeloid cell counts in the bone marrow.

B. Title: Naloxone Reversal of the Sedative Effects of an Overdose of Topical Fentanyl in Dogs (Ricerca Study No. 021590).

A non-clinical laboratory safety study was conducted under GLP by Dr. Michael C. Savides at Ricerca Biosciences, LLC, in Concord, OH. The purpose of this study was to test an intramuscular (IM) naloxone regime to reverse the narcotic effects of a 5X (13 mg/kg) overdose of transdermal fentanyl solution (final market formulation) in dogs. The study used 24 Beagle dogs, 4 dogs per sex in Group 1 and 8 dogs per sex in Group 2. All animals received a 13 mg/kg topical fentanyl dose to the ventral abdomen on Day 0. Dogs in Groups 1 and 2 received 0.04 and 0.16 mg/kg intramuscular (IM) naloxone doses, respectively, at 16 hours after fentanyl administration and hourly thereafter for a total of eight IM naloxone administrations per dog.

Sedation scoring, rectal temperature, and heart rate (HR) response measurements were conducted on all dogs at before and after each naloxone dose. In addition, sedation, rectal temperature, and HR measurements were collected at -1, 0, 14, 15, 24, 26, and 28 hours post-fentanyl dose. A single trained observer, masked to animal treatment, conducted all sedation scoring.

Increased sedation, decreased heart rate, and decreased body temperature were observed following the fentanyl dose during the first 16 hours. Hourly administrations of 0.04 and 0.16 mg/kg IM naloxone were effective at temporarily reversing the narcotic effects of a 5X overdose (13 mg/kg) of a transdermal fentanyl solution applied to the ventral abdomen of dogs. The 0.16 mg/kg IM naloxone dose was more effective than the 0.04 mg/kg dose at reducing the sedative, hypothermic, and bradycardic effects of a 5X overdose of fentanyl.

C. Title: PRO01-C-01: Non-clinical Laboratory Study: Evaluation of the Safety of a Topical Fentanyl Solution in Mongrel Dogs over 16 Weeks

1. Type of Study: Non-Clinical Laboratory Study conducted under GLP

2. Investigator: Craig Reinemeyer
East Tennessee Clinical Research, Inc.
Rockwood, TN 37854

3. General Design:

a. Purpose: To evaluate the chronic safety of RECUVYRA when administered to mongrel dogs at 0, 2.6 (1X), 5.2 (2X) and 7.8 mg/kg (3X) at a 7 day dosing interval for 16 weeks.

b. Test Animals: Eighteen purpose-bred mongrel dogs (9 male, 9 female).

c. Control: Saline administered topically at the 3X dose group volume.

d. Fentanyl: Final market formulation of RECUVYRA (transdermal fentanyl solution at 50 mg/mL).

e. Route of administration: Topical (transdermal by the dorsal scapular region).

f. Dosages used:

Table 22. Dose Groups for 7-Day Dose Interval, 16 Week Repeat Dose Study

Dose Group	Dose (mg/kg/week)	Number and Sex of Dogs
1	0 (control)	1 male, 1 female
2	2.6 (1X)	4 male, 4 female
3	5.2 (2X)	2 male, 2 female
4	7.8 (3X)	2 male, 2 female

Dogs were weighed on each dosing day to determine the dose of test article to administer.

g. Test duration: Sixteen weeks.

h. Parameters measured: Physical examinations, general health observations, clinical observations (sedation score, temperature, pulse, respiration, etc.), body weight, appetite, feces examination, hematology, serum chemistry, plasma fentanyl concentrations, and necropsy (including gross and histopathology examinations) following euthanasia at the end of 16 weeks.

Sedation was scored as follows:

0 - No Sedation Present
1 - Slight Sedation - almost normal; able to stand easily, but appears somewhat fatigued, subdued or somnolent.
2 - Moderate Sedation - able to stand but prefers to be recumbent; sluggish; ataxic or uncoordinated.
3 - Profound Sedation - unable to rise, but can exhibit some awareness of environment; responds to stimuli through body movement; may be lateral or sternal recumbency.
4 - Unresponsive - in a state of coma or semi-coma from which little or no response can be elicited; remains in lateral recumbency.

i. Statistical methods: Descriptive statistics (mean, standard deviation, minimum and maximum) were used to summarize the data. The existence or non-existence of treatment related effects could not be statistically determined due to the small sample size of study treatment groups.

j. Fentanyl assays: Blood samples were collected for plasma fentanyl assay from all dogs within one hour prior to dosing on days 0, 7, 14, 21, 28, and 105; and at 1, 8, 24, and 96 hours after the dose on days 0, 28, and 105.

A final blood sample was collected from each dog on day 112. Plasma was harvested and stored frozen at -20oC until assayed. The plasma samples were assayed using a validated LC/MS/MS method.

4. Results:

a. Clinical abnormalities:

There were no deaths in this study, and no concomitant drugs were used during the study. Animals were observed for abnormal health 3 times on dosing days and twice daily on all other study days. The most frequent adverse reactions were diarrhea, sedation, and weight loss (sedation score results are discussed under Physiological Abnormalities below). Other observed abnormalities are listed with diarrhea, sedation, and weight loss:

Table 23: Adverse reactions during the 16 week TAS study

Adverse Reactions
Aggression
Application site hair change
Application site pruritus
Ataxia
Dermatitis
Diarrhea
Emesis
Erythema
Excoriation/pruritus
Hemorrhagic diarrhea/melena
Hyperactivity
Hypersalivation
Inappetance
Lethargy
Sedation
Skin abscess
Vocalization
Weight loss

1) Diarrhea: Diarrhea occurred frequently during the study in all dose groups including the 2 control dogs. Diarrhea was more frequently observed in fentanyl-treated dogs. Diarrhea did not show any tolerance over time, because the dogs did not show less sensitivity to the gastrointestinal effects of fentanyl over the 16 weeks of the study. Of the total number of diarrhea observations over the entire 16 weeks of the study (545 among 18 dogs), each treatment group showed the following number of diarrhea observations:

0X = 31 in 2 dogs
1X = 217 in 8 dogs
2X = 115 in 4 dogs
3X = 182 in 4 dogs

Some dogs in the treated groups had blood in the feces, hemorrhagic diarrhea, or melena listed as observations. In the 1X group, 1/8 dogs had 3 consecutive days of bloody feces, melena, or bloody diarrhea. In the 2X group, 2/4 dogs had fecal abnormalities: 1 dog had 3 consecutive days of melena with blood or bloody diarrhea, and 1 dog had a single observation of bloody diarrhea during week 1. In the 3X group, 1 dog had 2 consecutive days of bloody diarrhea.

Gastrointestinal abnormalities, observed sedation, and hyperactivity occurred commonly in the study. There was a large amount of variation in the frequency of diarrhea among dogs that received the same dose. Diarrhea was not definitively associated with fentanyl dose level. The following table shows the calculated average number of diarrhea observations per dog in each dose group:

Table 24: Average number of diarrhea observations by dog by treatment group

Treatment group	Average observations/dog
0X	15.5 observations/dog
1X	27.1 observations/dog
2X	28.8 observations/dog
3X	45.5 observations/dog

Four dogs showed blood in the stool, hemorrhagic diarrhea or melena as well as diarrhea. The table below shows other associated abnormalities in dogs with blood in the stool.

Table 25: Number of abnormal observations for dogs with blood in the stool

ID#	Tx Group	Blood in stool	Diarrhea, loose stool	Sedation	Emesis	Hyperactive Restless Agitated	Inappetance
686972	1X	3	18	9	3	6	3
703371	2X	3	42	37	1	0	7
698334	3X	2	82	30	0	1	4
699861	3X	2 (+tenesmus 1)	56	18	1	1	4

2) Inappetance and weight loss:

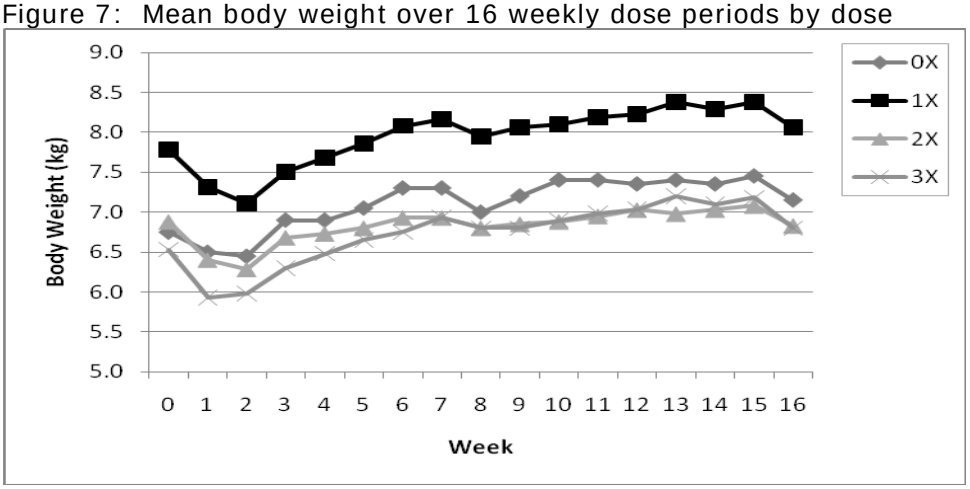
Decreased appetite appeared to be dose-dependent with greater incidences occurring in the higher dose groups.

Maximal weight loss occurred during the first and second weeks of the study; weights then stabilized, returning to pre-treatment weights by the fifth dose. Weight loss did not correlate with inability to eat associated with sedation. In the 1X group (8 dogs), weight loss ranged from 5.2-15.8% of initial body weight (compared to 1.7-6.5% in the 2 control dogs). Five of 8 1X dogs lost 5-10%; 2 lost 10-15%; 1 lost 15-20% of body weight compared to baseline.

Table 26: Number of dogs (%) showing weight loss after 1st and 2nd doses by treatment group

Body Weight Loss	Group 0X (n=2) Number (%)	Group 1X (n=8) Number (%)	Group 2X (n=4) Number (%)	Group 3X (n=4) Number (%)
Weight loss (0-5%)	1 dog (50%)	0	0	0
Weight loss (5%-10%)	1 (50%)	5 (62.5%)	3 (75%)	3 (75%)
Weight loss (10%-15%)	0	2 (25%)	0	0
Weight loss (15-21%)	0	1 (12.5%)	1 (25%)	1 (25%)

Figure 7: Mean body weight over 16 weekly dose periods by dose



b. Physiological abnormalities:

1) Sedation: Sedation was observed in each dose group after each dose. Dogs in the 1X group showed maximal sedative observations on the second and third days after the first dose (compared to the day of dosing). Signs of sedation after each fentanyl dose decreased by the second day in the 1X group and by day 3 in the 2X and 3X groups. The frequency of sedation observations decreased during the later weeks of the study, especially in the 1X dose group.

Mean sedation scores were higher during the first few dose intervals than in the subsequent dose intervals showing the development of tolerance to sedation.

The list below uses twice-daily sedation scores (none, slight, moderate, profound, unresponsive) by day after dosing to determine the percentage of dogs in the 1X dose group (8 dogs) that showed various levels of sedation after the first 7 weekly doses in the study. Some dogs in the 1X dose group became moderately sedated on days 2 and 3 after the first dose, even though they were only slightly sedated on the day of dosing.

1X: First dose:
a. 100% of dogs were slightly sedated on the first dosing day (day 1).
b. 25% were moderately sedated on the day after dosing (day 2).
c. 12.5% remained moderately sedated on day 3.
d. 25% were slightly sedated on day 4.
e. 12.5% were slightly sedated on day 5.

1X: Second dose:
a. 100% were slightly sedated on the first dosing day (day 1).
b. 100% were slightly sedated on day 2.
c. 50% were slightly sedated on day 3.

1X: Third dose:
a. 75% were slightly sedated and 12.5% were moderately sedated on day 1.
b. 50% were slightly sedated on day 2.
c. 12.5% were slightly sedated on day 3.

1X: Fourth dose:
a. 12.5% were slightly sedated on day 1.
b. 12.5% were slightly sedated on day 2.

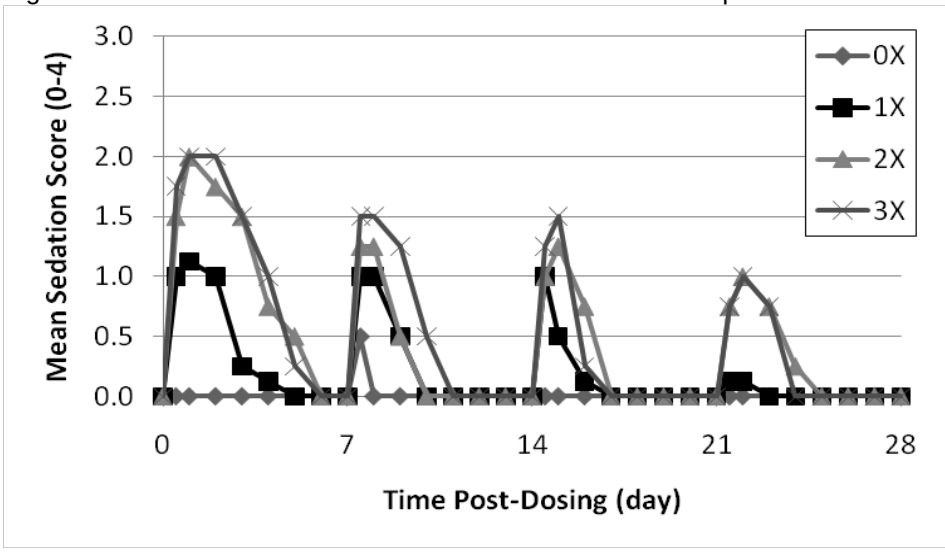
1X: Fifth dose:
a. 12.5% were slightly sedated on day 1.
b. 87.5% were slightly sedated on day 2.

1X: Sixth dose:
a. 25% were slightly sedated on day 1.
b. 37.5% were slightly sedated on day 2.
c. 25% were slightly sedated on day 3.

After the seventh dose (day 50), sedation was slight, seen in ≤ 25% of dogs in the 1X group, and observed only on the day of dosing ± the day after dosing. Mean sedation scores were numerically higher in the 2X and 3X groups than in the 1X group and scores also decreased with subsequent dosing intervals, supporting the development of tolerance to fentanyl's sedative effects in all dose groups.

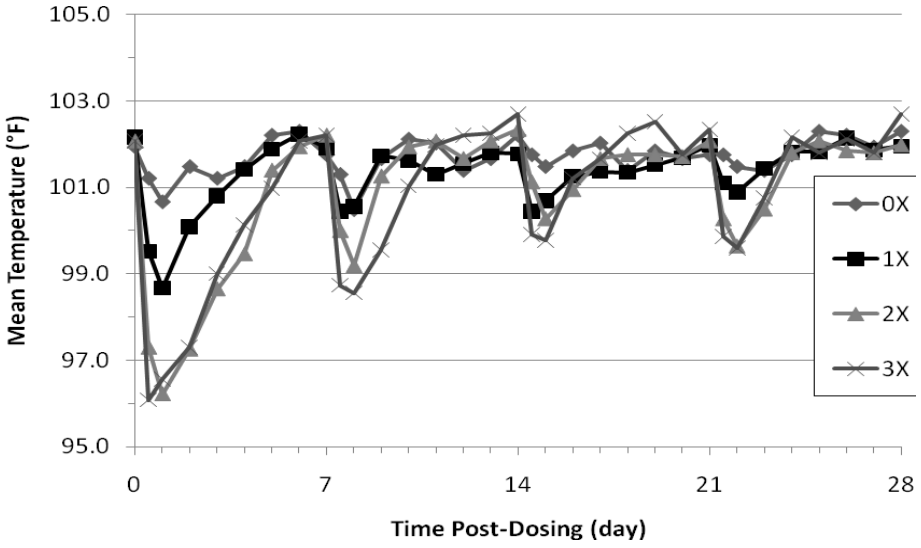
Finally, Figure 8 shows the mean sedation score fluctuations during the first 4 weeks of the study.

Figure 8: Mean sedation scores over the first 4 dose periods



2) Temperature: The day after dosing showed the greatest overall decreases in individual body temperature. Mean body temperatures decreased following each dose compared to the control group. There was evidence of tolerance to the effects of fentanyl on body temperature because the decrease in the mean was greater after the first dose compared to subsequent doses. The lowest temperature after the first dose was 33.9 °C (2X dose group). Some dogs received thermal support during the study; however, no hot water bottles were used for 1X dogs during the study (see Supportive Therapy section below). The lowest temperature in the 1X group on days 2 and 3 after the first dose was 99 ºF.

Figure 9: Mean body temperature over the first 4 dose periods



3) Heart rate (HR): In all treated groups, the maximal fentanyl effects (bradycardia <60 bpm) were recorded on the day of dosing and the day after fentanyl was administered. HR decreased within the 12 hours following the initial fentanyl dose. HR was lower on the day after dosing compared to 12 hours after the administration of fentanyl. Bradycardia was more pronounced in the 2X and 3X dose groups.

In the 1X group, the means remained above 70 bpm except for after the first dose (mean = 68 bpm). After doses 1, 2, 3, 8, and 15, some dogs in the 1X experienced HR < 60 bpm (lowest = 48 bpm). In the 2X and 3X groups, the lowest HR was noted after dose 1 (32 bpm). Other than that timepoint, the lowest recorded HR in any group at any time was 52. Comparatively, the lowest HR in the 0X group was 68 bpm.

4) Respiratory rate (RR): The maximal fentanyl effects on RR were recorded on the second day after dosing. The lowest RR in the 2X group was 16 breaths/min (for several doses); in the 1X and 3X groups, the lowest RR was 12 breaths/min on the second day after the first dose. In the 1X group, RR of 12 was also recorded after doses 3 and 13; and after the first dose in the 3X group.

Heart rate and respiration rate results did not definitively demonstrate opioid tolerance; however, the largest decreases in HR and RR occurred after the first dose, generally lessening over time with subsequent doses.

c. Supportive treatment:

Moderate levels of supportive therapy were administered to some dogs in the 1X, 2X, and 3X treatment groups. Two control dogs (of 2) and 1 dog in the 1X group received no supportive therapy during this study. The

types of supportive therapy were divided into 6 categories. These included: 1) offering highly palatable canned food if a dog was not eating sufficient kibble, 2) administration of 200 mL of subcutaneous fluids if a dog was not drinking sufficient water, 3) providing towels if a dog was spending more time lying down, 4) providing a hot water bottle or heating pad if a dog's ears felt cool, and 5) application of ocular lubrication if the dog was persistently sedated. Additional supportive therapies were administered as needed.

Towels, canned food, and fluid therapy were administered to dogs in the 1X dose group for weight loss, hypothermia, and moderate sedation. Canned food was provided to most fentanyl-treated dogs during the first 2 weeks of treatment. Supplemental bedding was also provided to most fentanyl-treated dogs and once initiated, was usually provided for the remainder of the study. Canned food was not required for any dog after the first two weeks of treatment except for one dog in the 1X group. It was noted on day 28 that this dog had lost weight, dropping from 8.4 kg to 7.5 kg. The dog began receiving 1 can of moist canned food per day on day 28, and it maintained its weight on this diet through the remainder of the study. This dog was never observed or scored as sedated, and vital signs were satisfactory throughout the study. A different dog in the 1X group was administered fluids. This dog was slightly sedated and hypothermic (37.6 – 37.8 °C) in the evening after the second treatment (day 15) and again the following morning. It was provided with a towel for the remainder of the study and given fluids once on day 15. No other therapy was provided after this day. Dogs in the higher dose groups required more supportive care compared to the 1X dose group.

d. Clinical Pathology: Blood samples were taken at baseline, every 7 days (on all dosing days prior to dosing), and at study conclusion on Day 112. Thirteen dogs overall showed mildly elevated WBC counts, including 3 of the 4 dogs with blood in the stool (the 1X dog with bloody stool did not show increases in WBC count). Four dogs had WBC elevations during week 1 (0X, 1X, and 2X groups), and 2 dogs during week 2 (0X and 3X). There was no correlation between WBC elevations and dose group or week of the study. Although most mean values were within the normal range for each clinical pathology variable, there were mild decreases in mean HGB (hemoglobin) and MCHC (mean corpuscular hemoglobin concentration), and mild increases in mean MCV (mean corpuscular volume) and platelet counts. These results could not be statistically analyzed due to low numbers of subjects in most treatment groups. Evaluations for coagulation variables, reticulocyte counts, and fibrinogen were not conducted.

e. Necropsy: A greater number of gross lesions were noted in dogs dosed at 3X; however, the pathologist stated that the lesions (hydrocephalus, changes to the right AV valve, and thyroid asymmetry) were not likely to have been caused by fentanyl. After 16 weeks of weekly fentanyl administration, minimal and reversible fentanyl treatment-related histological changes were noted in the liver (liver cell pigmentation, microgranuloma) and in the skin (epidermal inflammation) at doses $\geq$ 2X. Bone marrow was not evaluated.

f. Fentanyl Assays: Plasma fentanyl exposure increased proportionally with each dose through the fourth dose interval, reaching steady-state plasma fentanyl concentrations by the fifteenth dose interval in the 1X group.

5. Conclusions for 16 week TAS study: Administration of RECUVYRA at the recommended dose every 7 days was well tolerated by dogs receiving moderate supportive therapy to prevent severe weight loss, hypothermia, and dehydration (canned food for weight loss, towels and hot water bottles for decreased body temperatures, and subcutaneous fluids for dehydration). Sedation was observed more frequently on the day after dosing, was related to dose, and decreased in frequency and intensity with repeated doses of transdermal fentanyl (opioid tolerance). Feces abnormalities (diarrhea, blood in stool), decreased appetite, and/or weight loss were observed at some timepoint in most fentanyl treated dogs. Bodyweight decreases returned to pre-treatment weights by the fifth dose. Heart rate, respiration rate, and body temperature all decreased in fentanyl treated dogs. The magnitude of decreases in temperature, heart rate, and respiration rate lessened over time suggesting the development of tolerance. Decreased heart and respiratory rates were not related to fentanyl dose levels in this study. Plasma fentanyl exposure increased proportionally with each dose through the fourth dose interval, reaching steady-state plasma fentanyl concentrations by the fifteenth dose interval in the 1X group.

D. Title: ARDG01-C-04: Clinical Study: Evaluation of the Efficacy and Safety of a Topical Fentanyl Solution when used for Postoperative Pain following Soft Tissue Surgery in Dogs

1. Type of Study: Field Study (conducted under VICH-GCP)

Study results were evaluated for field safety data. The study was not evaluated for effectiveness.

2. Investigators and Study Locations:

Table 27: Investigators and Study Locations

Prof. Leo Brunnberg Berlin, Germany	Dr Sabine Tacke Giessen, Germany
Dr Sabine Kramer Hannover, Germany	Dr Michaele Alef Leipzig, Germany
Dr Matthias Vick Oldenburg, Germany	Dr Wolf-Rainer Seeburg Hamburg, Germany
Dr Alexander Koch Embsen-Oerzen, Germany	Dr Inke Christiansen Steinbergkirche, Germany
Dr Bernadette Hartmann Lüdinghausen, Germany	Dr. Ute Altmann Büren, Germany
Alexandre Guillemot Nantes, France	Cyrill Poncet Arcueil, France
Marc Giry Charbonnieres les Bains, France	Michel Dubor Lyon, France
Pierre Lemaire Pontault Combault, France	Silja Cahen Reims, France
Stephan Mangin Thorigny sur Marne, France	Stephane Libermann Meaux, France
Xavier Ferreira Strasbourg, France	Serge Monnier Saint Etienne, France
Valérie Guérin-Guigardet Reyrieux, France	Scott Dickson Edinburgh, UK
Alan Mayo Cheshire, UK	Mr Iain Richards Kendal, Cumbria, UK
Ann Noble Carlisle, UK	Mr David Young Alnwick, UK
Mr John Smith Ripon, North Yorkshire, UK	Mr John Boyle Cockermouth, Cumbria, UK
Adele Trott Dewsbury, West Yorkshire, UK	

3. General Design:

a. Purpose: To evaluate the clinical effectiveness and safety and of RECUVYRA (based on clinical assessment of post-operative pain) following soft tissue surgery in dogs.

b. Test Animals: Two hundred thirty-five dogs were enrolled: 119 dogs received topical fentanyl solution (2.6 mg/kg to the dorsal scapular area 2-4 hours prior to intubation) and 116 received buprenorphine. Approximately 38% of the total surgery types were ovariohysterectomy. The other surgery types included: mammary tumors (~17%), anal sac removal (~8%), cryptorchid/retained testes removal (~6%), cystotomy (~5%), perineal hernia (~5%), lateral ear resection (~5%), enterotomy (~3%), splenectomy (~3%), total ear ablation (~3%), pyometra (~3%), kidney removal/biopsy (~2%), laparotomy including tumor removal (~1%), and liver lobectomy/biopsy (~1%).

c. Control: The active control was buprenorphine hydrochloride injection administered intramuscularly in the dorsal scapular region 2 – 4 hours prior to surgery, at the time of extubation, and every 6 hours through and including 90 hours post-extubation.

d. Fentanyl: Final market formulation of RECUVYRA (fentanyl solution at 50 mg/mL).

e. Route of administration (RECUVYRA): Topical (transdermal by the dorsal scapular region).

f. Dosages used: Dogs randomized to RECUVYRA received a single, dermal, topical application on the dorsal scapular area approximately 2 – 4 hours prior to surgery according to the following dosing table:

Table 28: Fentanyl Dosing Table (lb, kg and mL)

Body weight		
Lbs	Kgs	Dose (mL)
6.0 to 9.3	3.0 to 4.2	0.2
9.4 to 13.4	4.3 to 6.1	0.3
13.5 to 17.6	6.2 to 8.0	0.4
17.7 to 21.8	8.1 to 9.9	0.5
21.9 to 25.9	10.0 to 11.7	0.6
26.0 to 30.1	11.8 to 13.6	0.7
30.2 to 34.3	13.7 to 15.5	0.8
34.4 to 38.4	15.6 to 17.4	0.9
38.5 to 42.6	17.5 to 19.3	1.0
42.7 to 46.8	19.4 to 21.2	1.1
46.9 to 50.9	21.3 to 23.1	1.2
51.0 to 55.1	23.2 to 25.0	1.3
55.2 to 59.3	25.1 to 26.9	1.4
59.4 to 63.4	27.0 to 28.8	1.5
63.5 to 67.6	28.9 to 30.6	1.6
67.7 to 71.8	30.7 to 32.5	1.7
71.9 to 75.9	32.6 to 34.4	1.8
76.0 to 80.1	34.5 to 36.3	1.9
80.2 to 84.3	36.4 to 38.2	2.0
84.4 to 88.4	38.3 to 40.1	2.1
88.5 to 92.6	40.2 to 42.0	2.2
92.7 to 96.8	42.1 to 43.9	2.3
96.9 to 100.9	44.0 to 45.8	2.4
101.0 to 105.1	45.9 to 47.7	2.5
105.2 to 109.3	47.8 to 49.6	2.6
109.4 to 113.4	49.7 to 51.4	2.7
113.5 to 117.6	51.5 to 53.3	2.8
117.7 to 121.8	53.4 to 55.2	2.9
121.9 to 125.0	55.3 to 57.1	3.0

g. Test duration: Four days (96 hours) for each study animal

h. Parameters measured: Physical examinations, body weight, hematology, serum chemistry, pain assessments, and clinical observations were evaluated at 1, 2, 4, 6, 8, and 12 hours post-extubation on day 1, twice daily on days 2-4, and once on day 5. Dogs were hospitalized during the 5 study days. Anesthetic regimes included various combinations of preanesthetics (glycopyrrolate, atropine, acepromazine, diazepam, midazolam), induction agents (propofol, thiopental, ketamine), and isoflurane.

4. Safety Results:

Adverse events were reported in 31 RECUVYRA-treated dogs (26.1%) and 25 buprenorphine-treated dogs (21.6%). These adverse events are itemized by category as follows:

Table 29: Adverse Reactions

Category	RECUVYRA (N=119)	Buprenorphine (N=116)
Diarrhea	8 (6.7%)	5 (4.3%)
Emesis	8 (6.7%)	5 (4.3%)
Sedation	6 (5.0%)	1 (0.9%)
Anorexia	5 (4.2%)	3 (2.6%)
Ataxia	4 (3.4%)	0 (0.0%)
Conjunctivitis	3 (2.5%)	3 (2.6%)
Hypersalivation	3 (2.5%)	1 (0.9%)
Hypothermia	2 (1.7%)	4 (3.4%)
Tenesmus	2 (1.7%)	2 (1.7%)
Urine Abnormalities	1 (0.8%)	1 (0.9%)
Abnormal Test Result	1 (0.8%)	0 (0.0%)
Anemia	1 (0.8%)	0 (0.0%)
Arrhythmia	1 (0.8%)	0 (0.0%)
Ascites	1 (0.8%)	0 (0.0%)
Death	1 (0.8%)	0 (0.0%)
Dermatitis	1 (0.8%)	0 (0.0%)
Dyspnea	1 (0.8%)	0 (0.0%)
Eye Inflammation	1 (0.8%)	0 (0.0%)
Musculoskeletal Disorder	1 (0.8%)	0 (0.0%)
Protrusion membrane nictitans	1 (0.8%)	0 (0.0%)
Pruritus	1 (0.8%)	0 (0.0%)
Pyrexia	1 (0.8%)	0 (0.0%)
Renal Failure	1 (0.8%)	0 (0.0%)
Urinary Bladder Disorder	1 (0.8%)	0 (0.0%)
Bradycardia	0 (0.0%)	2 (1.7%)
Nystagmus	0 (0.0%)	2 (1.7%)
Corneal Ulcer	0 (0.0%)	1 (0.9%)
Cranial Nerve Disorder	0 (0.0%)	1 (0.9%)
Gastritis	0 (0.0%)	1 (0.9%)
Hyperactivity	0 (0.0%)	1 (0.9%)
Keratoconjunctivitis sicca	0 (0.0%)	1 (0.9%)
Myoclonus	0 (0.0%)	1 (0.9%)
Stranguria	0 (0.0%)	1 (0.9%)
Tachycardia	0 (0.0%)	1 (0.9%)

Sedation scores were highest (moderate) at 1 hour post-extubation, decreasing to slight by the next day. Three fentanyl-treated dogs became moderately sedated between days 2-3, returning to slight sedation by the end of the third day.

Table 30: Number* of dogs and percent body weight loss by treatment group

Percent weight loss	Fentanyl group N = 114	Buprenorphine group N = 114
Weight Loss (>0-5%)	53 (46.5%)	45 (39.5%)
Weight Loss (>5% - 10%)	30 (26.3%)	30 (26.3%)
Weight Loss (>10% - 15%)	5 (4.4%)	6 (5.3%)
Weight Loss (>15%)	0 (0.0%)	1 (0.9%)

*Numbers do not include dogs removed from the study.

Adverse reactions were reported in thirty-one (of 119) fentanyl-treated dogs (26.1%) and 25 buprenorphine-treated dogs (21.6%). Diarrhea and emesis were the most frequently reported events, occurring in 6.7% of the fentanyl-treated dogs. Sedation, anorexia, ataxia, conjunctivitis, hypersalivation, hypothermia, and tenesmus were reported in 1.7-5.0% of the fentanyl dogs. All other events were reported at less than 1% for fentanyl-treated dogs.

Three fentanyl-treated dogs were removed from the study due a severe adverse reaction requiring naloxone reversal for ataxia, vomiting, and profound sedation (1 dog), lateral recumbency (unresponsive) for a second dog, and repeated vomiting for the third dog. One buprenorphine-treated dog was removed from the study due to repeated vomiting. Two fentanyl-treated dogs were reported with severe adverse reactions, but were not removed from the study: 1 for prolonged recovery and anemia due to disease (see below); and 1 with profound sedation and hypothermia for 48 hours.

One fentanyl-treated dog died during the study. The procedure was for liver lobectomy/biopsy. The dog recovered, and was proceeding on the study without incident when it was found dead on the morning of the fourth day after dosing. Necropsy indicated biliary duct perforation and associated peritonitis; death was not attributed to fentanyl.

Two fentanyl-treated dogs died following completion of the study. One dog was reported during the study with severe adverse reactions of prolonged recovery and anemia following ovariohysterectomy for glandular cystic hyperplasia. The dog died 6 days after surgery. The dog received supportive fluid therapy and antibiotics throughout the study, becoming anorectic and thin, with pale, icteric mucous membranes. A thoracic radiograph showed pleural effusion and 800 mLs of bloody fluid were removed on the day of death. Necropsy was refused. Histology of the uterus and ovaries removed during the ovariohysterectomy showed glandular cystic hyperplasia of the endometrium, endometriosis, and focal early stages of a well-differentiated carcinoma of the surface epithelium. The cause of death was not attributed to fentanyl.

Another dog had surgery for kidney removal/biopsy to diagnose underlying renal pathology. Biopsy results confirmed a renal hemangiosarcoma. At the first observation on day 1, the pain score was an 11 and the dog was

removed from the study due to lack of pain control. Following removal due to lack of pain control, the dog received morphine to control pain and supportive fluid therapy was continued for 8 days due to renal failure. The dog died 11 days following study completion and necropsy confirmed renal metastasis of a hemangiosarcoma. The cause of death was not attributed to fentanyl.

5. Conclusion: Under the study conditions, fentanyl transdermal solution demonstrated an adequate, although narrow, margin of safety.

E. Title: ARDG01-C-05: Clinical Study: Evaluation of the Efficacy and Safety of a Topical Fentanyl Solution when used for Postoperative Pain following Cruciate Repair Surgery in Dogs

1. Type of Study: Field Study (conducted under VICH-GCP)

Study results were evaluated for field safety data of transdermal fentanyl. The study was not evaluated for effectiveness.

2. Investigators and Study Locations:

Table 31: Investigators and Study Locations

Prof. Leo Brunnberg Berlin, Germany	Dr Sabine Tacke Giessen, Germany
Dr Sabine Kramer Hannover, Germany	Dr Michaele Alef Leipzig, Germany
Dr Matthias Vick Oldenburg, Germany	Dr Wolf-Rainer Seeburg Hamburg, Germany
Dr Alexander Koch Embsen-Oerzen, Germany	Dr Inke Christiansen Steinbergkirche, Germany
Dr Bernadette Hartmann Lüdinghausen, Germany	Cyrill Poncet Arcueil, France
Alexandre Guillemot Nantes, France	Michel Dubor Lyon, France
Marc Giry Charbonnieres les Bains, France	Silja Cahen Reims, France
Pierre Lemaire Pontault Combault, France	Stephane Libermann Meaux, France
Stephan Mangin Thorigny sur Marne, France	Serge Monnier Saint Etienne, France
Xavier Ferreira Strasbourg, France	Charlie Sale Cheshire, UK
Thierry Dembour Ollioules, France	Alan Mayo Nantwich, Cheshire, UK
Briony Alderson West Yorks, UK	Scott Dickson Edinburgh, UK
Harry Scott Ringwood, Hampshire, UK	Adele Trott Dewsbury, West Yorkshire, UK

3. General Design:

a. Purpose: To evaluate the clinical effectiveness and safety of RECUVYRA (based on clinical assessment of post-operative pain) following orthopedic surgery in dogs.

b. Test Animals: Two hundred and ten (210) animals were enrolled and received at least one treatment in this study. Animals enrolled in the study included 91 males and 119 females. Of these, 54 were intact males, 37 were castrated males, 49 were intact females, and 70 were spayed females, ranging in age from 0.6 – 15 years. Approximately 87% of the dogs were purebred. Over half of the dogs (61%) received cruciate repair via fabellar suture. Another 27% were repaired by tibial plateau leveling osteotomy (TPLO) and the remaining 12% were corrected by tibial tuberosity advancement (TTA). Dogs were hospitalized during the 5 study days. Anesthetic regimens included various combinations of premedicants (glycopyrrolate), preanesthetics (acepromazine, diazepam, midazolam), induction agents (propofol, thiopental, ketamine), and isoflurane.

c. Control: The positive control veterinary product was buprenorphine hydrochloride injection (Vetergesic®), administered intramuscularly in the dorsal scapular region 2 – 4 hours prior to surgery, at the time of extubation, and every 6 hours through and including 90 hours post-extubation.

d. Fentanyl: Final market formulation of RECUVYRA (fentanyl solution at 50 mg/mL).

e. Route of administration (RECUVYRA): Topical (transdermal via the dorsal scapular region).

   Dosages used: Dog randomized to RECUVYRA received a single, dermal, topical application on the dorsal scapular area approximately 2 – 4 hours prior to surgery according to the following dosing table:

Table 32: Fentanyl Dosing Table (lb, kg and mL)

Body weight		Dose
Lbs	Kgs	mL
6.0 to 9.3	3.0 to 4.2	0.2
9.4 to 13.4	4.3 to 6.1	0.3
13.5 to 17.6	6.2 to 8.0	0.4
17.7 to 21.8	8.1 to 9.9	0.5
21.9 to 25.9	10.0 to 11.7	0.6
26.0 to 30.1	11.8 to 13.6	0.7
30.2 to 34.3	13.7 to 15.5	0.8
34.4 to 38.4	15.6 to 17.4	0.9
38.5 to 42.6	17.5 to 19.3	1.0
42.7 to 46.8	19.4 to 21.2	1.1
46.9 to 50.9	21.3 to 23.1	1.2
51.0 to 55.1	23.2 to 25.0	1.3
55.2 to 59.3	25.1 to 26.9	1.4
59.4 to 63.4	27.0 to 28.8	1.5
63.5 to 67.6	28.9 to 30.6	1.6
67.7 to 71.8	30.7 to 32.5	1.7
71.9 to 75.9	32.6 to 34.4	1.8
76.0 to 80.1	34.5 to 36.3	1.9
80.2 to 84.3	36.4 to 38.2	2.0
84.4 to 88.4	38.3 to 40.1	2.1
88.5 to 92.6	40.2 to 42.0	2.2
92.7 to 96.8	42.1 to 43.9	2.3
96.9 to 100.9	44.0 to 45.8	2.4
101.0 to 105.1	45.9 to 47.7	2.5
105.2 to 109.3	47.8 to 49.6	2.6
109.4 to 113.4	49.7 to 51.4	2.7
113.5 to 117.6	51.5 to 53.3	2.8
117.7 to 121.8	53.4 to 55.2	2.9
121.9 to 125.0	55.3 to 57.1	3.0

f. Test duration: Four days (96 hours) for each study animal.

g. Parameters measured: Physical examinations, body weight, hematology, serum chemistry, pain assessments, and clinical observations at each pain assessment (sedation score, temperature, pulse, respiration, and lens opacity). Safety assessments included sedation, temperature, pulse, and respiration and were evaluated at 1, 2, 4, 6, 8, and 12 hours post-extubation on day 1, twice daily on days 2-4, and once on day 5.

4. Safety Results:

Adverse events were reported in 16 RECUVYRA-treated dogs (15.4%) and 23 buprenorphine-treated dogs (21.7%). These adverse events are itemized by category as follows:

Table 33: Adverse Reactions

Category	Fentanyl (N=104)	Buprenorphine (N=106)
Emesis	4 (3.8%)	6 (5.7%)
Bradycardia	3 (2.9%)	3 (2.8%)
Anorexia	2 (1.9%)	5 (4.7%)
Sedation	2 (1.9%)	2 (1.9%)
Diarrhea	1 (1.0%)	4 (3.8%)
Tachycardia	1 (1.0%)	2 (1.9%)
Abnormal Test Result	1 (1.0%)	0 (0.0%)
Aggression	1 (1.0%)	0 (0.0%)
Anuria	1 (1.0%)	0 (0.0%)
Cardiac Arrest	1 (1.0%)	0 (0.0%)
Hypersalivation	1 (1.0%)	0 (0.0%)
Hypertension	1 (1.0%)	0 (0.0%)
Hypothermia	1 (1.0%)	0 (0.0%)
Intestinal Stasis	1 (1.0%)	0 (0.0%)
Localized Pain	1 (1.0%)	0 (0.0%)
Otitis	1 (1.0%)	0 (0.0%)
Skin Edema	1 (1.0%)	0 (0.0%)
Tachypnea	1 (1.0%)	0 (0.0%)
Loss of Condition	1 (1.0%)	0 (0.0%)
Conjunctivitis	0 (0.0%)	1 (0.9%)
Corneal Ulcer	0 (0.0%)	1 (0.9%)
Hyperactivity	0 (0.0%)	1 (0.9%)
Metritis	0 (0.0%)	1 (0.9%)
Muscle Tremor	0 (0.0%)	1 (0.9%)
Polydipsia	0 (0.0%)	1 (0.9%)
Tenesmus	0 (0.0%)	1 (0.9%)

Sedation scores were highest (moderate) at 1 hour post-extubation in both treatment groups. By 6 hours post-extubation, dogs in both groups were scored as slightly sedated. Three fentanyl-treated dogs increased to moderate or higher sedation on days 2 and 3. By day 4, none of the fentanyl-treated dogs were more than slightly sedated.

Table 34: Number* of dogs and percent body weight loss by treatment group

Percent weight loss	Fentanyl (N=100)	Buprenorphine (N=104)
Weight Loss (>0-5%)	47 (47.0%)	44 (42.3%)
Weight Loss (>5% - 10%)	23 (23.0%)	26 (25.0%)
Weight Loss (>10% - 15%)	4 (4.0%)	4 (3.8%)

*Numbers do not include dogs removed from the study.

Adverse events were reported in 16 fentanyl-treated dogs (15.4%) and 23 buprenorphine-treated dogs (21.7%). Emesis, bradycardia, anorexia, and sedation were the most frequently reported events, occurring in 1.9-3.8% of the fentanyl-treated dogs. All other events were reported at less than 1% for fentanyl-treated dogs.

Two dogs were removed from the study because of adverse reactions due to fentanyl: 1 with profound sedation (for 48 hours) and periods of bradycardia (40-100 bpm), and 1 with hypothermia (34.9 to 36.1°C), bradycardia (56-88 bpm), and lethargy for >48 hours. One buprenorphine-treated dog was removed from the study due to anorexia and lethargy. Another buprenorphine-treated dog showed severe hemorrhagic diarrhea, but was not removed from study.

One death occurred in a fentanyl-treated dog. The 46 kg dog received transdermal fentanyl 3 hours prior to anesthesia (acepromazine, thiopental, isoflurane). Fifteen minutes after induction the dog went into cardiac arrest, followed by respiratory arrest. Resuscitation procedures were unsuccessful and necropsy was unremarkable. The death was attributed to the barbiturate (thiopental).

5. Conclusion: Under the study conditions, fentanyl transdermal solution demonstrated an adequate, although narrow, margin of safety.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY:

A. Human User Safety Studies:

1. *In vitro study* 08-003-PRO1: This study demonstrates that latex or nitrile gloves protect the human user from accidental skin exposure to liquid transdermal fentanyl solution when handling and applying the solution to dogs. Therefore, labeling recommends that the human user wear latex or nitrile gloves when handling transdermal fentanyl solution.

2. Study 021594: The objective of this study was to determine the time that it takes for a vehicle formulation (formulation with all components except fentanyl) to dry after application to the abdomen of dogs. [Note that for bioavailability reasons, the approved application site is the dorsal scapula area.]

   Twenty male and 20 female Beagles (4.5-6.5 months old) were assigned to the study, with 5 dogs (2 of one sex and 3 of the other) in each of 8 groups. Each animal received the same volume as the 2.6 mg/kg dose for transdermal fentanyl solution. At 0.5, 1, 1.5, 2, 3, 4, 5, or 10 minutes following dosing, the application area was blotted once with a dry wipe. The wipe was visually inspected and documented as to whether it was wet or dry.

   All the observed wipes were wet from 0.5 to 2 minutes post-application. By 3 minutes, 80% of the wipes were dry, and by 5 minutes 100% of the wipes were dry. Therefore, the label recommends a drying time of 5 minutes following administration of transdermal fentanyl solution.

3. Study 020621A: The objective of this study was to determine the exposure of fentanyl in dogs when the liquid solution was intentionally applied sublingually. A total of 12 male and 12 female Beagle dogs of approximately 1-2 years of age were assigned to three groups of 8 dogs. The groups received a sublingual dose of liquid fentanyl solution (0.1 mg/mL) at a dose of 5, 10, or 20 mcg/kg. The dogs were observed daily. Blood was collected prior to dosing and at 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose to determine fentanyl concentrations.

   Absorption of fentanyl was rapid through mucous membranes, with mean maximal concentrations occurring between approximately 5 and 8 minutes, increasing proportionally by dose. This supports label warnings that state that oral or mucous membrane exposure to topical fentanyl solution could result in a hazard (plasma concentrations of fentanyl) to both dogs and humans.

4. Study 021593: The objective of this study was to determine the amount of fentanyl that could contact the human user from the dog dorsal scapula application site at various time intervals following the administration of 2.6 mg/kg topical fentanyl solution. In 40 dogs, the application area was wiped with a cotton glove in a manner similar to "petting" at the following time points: 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours post-application. Each cotton glove was extracted and analyzed for fentanyl concentrations.

   The amount of fentanyl recovered from the glove was most variable in the first 8 hours after administration. Immediately following application, 4.25% of the applied dose was estimated to be recovered from the glove. At 24 and 48 hours following dosing, approximately 2% and 1% of the applied dose, respectively, was transferred to the glove. The amount of fentanyl transferred declined over time with an estimated half-life of 23.3 hours. Therefore, the label warns that humans should avoid direct contact

with the treated dog for a minimum of 72 hours after application of transdermal fentanyl solution.

5. Study 021101: The objective of this study was to determine the bioavailability of fentanyl to undosed dogs that rub or lick the skin of dogs treated with transdermal fentanyl solution.

   In the first set of dogs, a 2.6 mg/kg dose of transdermal fentanyl solution was applied to the ventral abdomens of 6 dogs (group 1). Two hours following dosing, 6 experimentally naïve dogs (group 2) were exposed to the ventral surface of dosed dogs by directly rubbing their abdomens against the application site of treated dogs for 15-30 seconds. Elizabethan collars were placed on the naïve dogs to prevent access to their own abdomens. Blood samples were taken from naïve, untreated dogs prior to the transfer and at 12, 24, 36, 48, and 72 hours after rubbing the surfaces together.

   In a second set of dogs, a 2.6 mg/kg dose of transdermal fentanyl solution was applied to the ventral abdomens of 6 dogs. Two hours after dosing, 6 experimentally naïve dogs were exposed to the ventral surface of dosed dogs by licking the dosed area on the ventral surface of the 6 treated dogs. For dogs that did not lick the area, their noses were rubbed against the dosed area. Blood samples were taken from naïve dogs before the licking and at 5, 10, 15, 60 and 120 minutes after licking. Plasma samples from both the dermal and oral exposure dogs were analyzed for fentanyl concentrations.

   Results: Only a small amount of the applied 2.6 mg/kg transdermal fentanyl solution dose was transferred during skin to skin transfer. In the dermal transfer group, concentrations were low with approximately half of the samples having concentrations below the lower limit of quantification (< 0.025 ng/mL); the mean plasma fentanyl concentrations were below 0.1 ng/mL at all sampled times. However, following licking, plasma concentrations in naïve dogs may have entered the therapeutic range of fentanyl concentrations. The mean concentrations at each time point over 72 hours in these dogs ranged between 0.4 and 1.6 ng/mL in all sampled times following exposure.

   Conclusions: Direct skin-to-skin contact with the dried application site did not result in significant exposure of fentanyl to naïve dogs and are not expected to have any pharmacological effect. However, direct oral exposure to the application site could result in exposure to both dogs (and potentially humans) that could result in pharmacological effects. Therefore, the label recommends contacting a physician if oral exposure occurs in dogs or humans.

6. Study DDS03: These data came from a study that was conducted in support of the discontinued development of transdermal fentanyl solution for use in human beings. It compares the bioavailability and pharmacokinetics of an exploratory human formulation of transdermal fentanyl solution to the DURAGESIC patch. In a three-way crossover design, each of 6 human subjects (healthy males, aged 18 – 40) received

a single dose of transdermal fentanyl solution to the outer upper arm and outer thigh and a DURAGESIC patch to the outer upper arm in a randomized fashion. The dose of fentanyl applied to the arm and thigh were 5 X 55 µL sprays of 7.5% transdermal fentanyl solution. In conjunction, 25-50 mg of oral naltrexone were administered for 3 days. For the patch, a 25 µg/hour patch was applied for 72 hours in conjunction with daily 25-50 mg of oral naltrexone. Each treatment was separated by at least 11 days. Multiple blood samples were collected during each treatment period and analyzed for fentanyl.

The mean fentanyl Cmax for arm, thigh, and patch were 0.318, 0.0975, and 0.545 ng/mL respectively. The mean time to reach maximal plasma concentration (Tmax) for transdermal fentanyl solution was 34 hours (ranged from 18 to 96 hours). A total of 46 adverse events were reported by the six subjects that were administered a fentanyl treatment. Ten adverse events were deemed possibly related to the administration of fentanyl, 13 events were considered possibly related to naltrexone, and one event (somnolence) was considered possibly related to both transdermal fentanyl solution and naltrexone. Headache was the most commonly reported adverse event, which was reported on 7 occasions (15.2%) by 4 subjects (66.6%). On 6 occasions, 4 subjects experienced periods of somnolence considered related to fentanyl and/or naltrexone. All adverse events were mild or moderate in severity with the exception of a severe headache reported by one subject which was considered to be possibly related to naltrexone. No serious adverse events were reported.

The transdermal fentanyl solution used in this study was 17% more concentrated than RECUVYRA. Application to the human arm or thigh resulted in plasma concentrations of fentanyl that took up to 96 hours to peak (range 18 to 96 hours). Assuming linearity, applying a full milliliter of RECUVYRA solution to human skin could result in approximately 1.2 ng/mL peak plasma concentration approximately 1-3 days following exposure. Applying 3 mL of RECUVYRA solution (dose for a 57 kg dog) to human skin could result in 3.6 ng/mL peak plasma concentration 1-3 days following exposure.

Therefore, labeling states when accidental exposure of RECUVYRA solution to human skin occurs, medical evaluation should be sought promptly. To avoid direct contact with human skin while applying RECUVYRA solution to dogs, labeling states that humans should wear safety glasses, gloves, and a laboratory coat.

7. Study APO01: A human safety study was conducted to support the development of transdermal fentanyl solution for use in dogs titled, An Open Label, Phase I, Randomized, Parallel-Arm Trial in Healthy (human) Participants to Determine the Transfer Potential and Pharmacokinetics of Fentanyl Following Application of a Single Dose of Topical Fentanyl Solution to Dogs. This study used the same transdermal fentanyl formulation as the final market formulation.

   The objective of this study was to evaluate the potential oral transfer of fentanyl to adult humans who pet the application site of dogs, then

intentionally suck the fingers from the hand used for petting. A secondary analysis was conducted to estimate the potential plasma fentanyl concentrations and exposure in pediatric human subjects based on the adult human subject data.

Fifteen dogs were randomized to one of the fentanyl treatment time groups. The dogs received a single dose of transdermal fentanyl solution at 2.6 mg/kg on the dorsum between the shoulder blades using a proprietary applicator. A single human subject was randomized to a single dog in one of the treatment time groups. Each human subject had a single incidence of physical contact with a dog at the transfer time point. Human subjects directly petted the application site, by applying pressure with one open hand from the base of the dog's neck to mid thorax in a stroking motion 10 times over 30 seconds. After the petting was complete, each human subject sequentially placed all five digits of the hand used for petting, up to the middle interphalangeal joint, into the mouth and actively sucked each digit for 15 seconds. Blood samples were collected for fentanyl analysis from the human recipients pre-transfer and at 5, 10, 15, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after the placement of fingers in the mouth had been completed.

The results show that fentanyl is transferable to human handlers when fingers were sucked following a maximum of 30 seconds physical contact by petting at 0.25, 2, 8, 24, and 72 hours post topical application. Human systemic exposure was variable; however, the median Cmax is below 0.1 ng/mL for all exposure groups (0.1 ng/mL is considered the minimum therapeutic level for humans). As time between application and petting increased, human systemic exposure decreased.

Simulated fentanyl exposure in pediatric humans predicted greater exposure and therefore a potential greater safety hazard than that observed in adult humans if the hands are sucked following interaction with a treated dog's application site. Therefore, labeling states that children should avoid contact with the application site altogether for a minimum of 72 hours after transdermal fentanyl solution is applied to dogs. After any interaction with the application site, hands should not be inserted into the mouth, should be washed with soap and water, and a physician should be notified immediately.

8. Study NCY00-X-16: Topical Residual Fentanyl Post-Dosing Over Time. The objective of the study was to determine how re-wetting the application site affected the amount of topical residual fentanyl recovered using a cotton glove following a single administration of transdermal fentanyl solution to the dorsal scapular skin of dogs. Forty Beagle dogs were randomized to ten treatment groups containing 4 dogs per group. Prior to treatment on Day -1, the dorsal scapular application site of all dogs was wiped with a cotton glove to confirm that no fentanyl was present prior to dose administration. A single 2.7 mg/kg topical dose of transdermal fentanyl solution was applied to the skin of the dorsal scapular region to all dogs on Day 0. A second cotton glove wiping was conducted on each dog post-dosing according to the treatment randomization. Dogs in half the treatment groups (Groups 1W-5W) had

the application site re-wetted with distilled water using a spray bottle 5 minutes prior to cotton glove wiping, while the application site of dogs in the other treatment groups (Groups 1D-5D) remained dry. Groups 1D and 1W dogs were wiped on Day 0 at 8 hours post-dose administration. Dogs in Groups 2D/2W, 3D/3W, 4D/4W, and 5D/5W were wiped at 24, 48, 72, and 120 hours post-dose administration, respectively. Cotton gloves were assayed for fentanyl amounts using a validated analytical method with a lower limit of quantification (LLOQ) of 20 µg per glove. Summary statistics of the bodyweight normalized residual fentanyl amounts per glove were calculated by time and dry/re-wetted application site. A linear fixed effects model was fitted to the data to test the effect of re-wetting the application site on the bodyweight normalized residual fentanyl amounts.

No animals were removed and no deaths or adverse events occurred during the study. Fentanyl was not measureable (< LLOQ) on any of the pre-dose administration (Day -1) cotton glove samples. At 8 hours post-dosing the mean residual fentanyl amounts recovered from the cotton gloves were 1.52% and 1.31% of the nominal 2.7 mg/kg transdermal fentanyl solution dose, respectively. At 72 hours post-dosing, mean cotton glove residual amounts were 0.31% and 0.35% of the applied dose for dry and re-wetted application sites, respectively; and at 120 hours post-dosing, the mean residual amounts were < 0.28% and 0.19%, respectively.

There was no statistically significant main or interaction effect of the application site being dry or re-wetted immediately prior to cotton glove wiping on the residual fentanyl amounts ($P > 0.05$). It was concluded that re-wetting the application site had no effect on the amount of topical residual fentanyl wiped from the application site with a cotton glove following a single administration of transdermal fentanyl solution to dogs.

Overall conclusion on safety: The risk/benefit ratio is acceptable to support approval of RECUVYRA. RECUVYRA provides pain control for up to 4 days following surgical procedures in dogs. There are risks to both dogs and humans. The evaluation of these risks during the effectiveness field studies conducted in the USA and the EU provided evidence that the benefits outweigh the risks to dogs and humans. The margin of safety in the effectiveness field studies was satisfactory in dogs and no human adverse reactions were reported (including abuse). Adequate communication between the trained veterinarian, their employees, and the clients is essential to minimize involuntary exposure of fentanyl transdermal solution to humans in the clinic and in the home. This information is provided in labeling and through the sponsor's voluntary post-approval Risk MAP training and monitoring program.

B. User Safety Labeling:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to RECUVYRA, and regarding abuse potential.

WARNING:

Abuse Potential:
Recuvyra™ contains fentanyl, a high concentration μ-opioid receptor agonist (50 mg/mL) and is a Class II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Class II opioid substances have the highest potential for human abuse and criminal diversion. The high concentration of RECUVYRA may be a particular target for human abuse. Fentanyl has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Fatal fentanyl overdoses in humans are due to respiratory depression.

The risk of abuse by humans should be considered when storing, administering, and disposing of RECUVYRA. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (suicidal depression).

Risk Minimization and Action Plan:
This product is distributed under a Risk Minimization Action Plan (RiskMAP) and its use is limited to certified veterinarians.

Human Safety:
SECONDARY EXPOSURE TO FENTANYL IN CHILDREN AND ADULTS: Strict adherence to the requirements of the RiskMAP and the INSTRUCTIONS FOR USE provided in this product insert is imperative in order to reduce the potential of secondary exposure to fentanyl from RECUVYRA treated skin.

•The dog should be isolated from children for 72 hours (3 days) from the time of RECUVYRA application to the dog.

•If a child comes in direct contact with the application site within 72 hours (3 days) from the time of RECUVYRA application to the dog, the exposed area should not contact the child's mouth or eyes, and the exposed area should be washed with soap and water.

•If a child's tongue comes in contact with the dog, or another part of the child's body comes in contact with the dog and is then placed in the mouth, it is possible for fentanyl to enter the bloodstream; this is a medical emergency and the child should be seen immediately by a physician.

•Adults should avoid contact with the application site for 72 hours (3 days) following the application of RECUVYRA to the dog. Within this period, any part of the body that directly contacts the application site should be washed with soap and not inserted into the mouth.

•The antidote for human exposure to RECUVYRA transdermal solution is an opioid reversal agent such as naltrexone or naloxone.

Risk Minimization & Action Plan:
The RECUVYRA Risk Minimization Action Plan (RiskMAP) provides educational materials to the veterinarian, veterinary staff, and the dog owner explaining the risks and proper use of RECUVYRA. Once it is documented that the dog owner has read and understood the materials by signing the client information sheet, the drug can be applied to the patient. Veterinarians are expected to report all serious adverse events that occur in animals or humans to the manufacturer (see WARNINGS).

RECUVYRA is only for use in dogs, and available only through a restricted distribution program limited to certified distributors that are trained to distribute RECUVYRA under the conditions of the RiskMAP. RECUVYRA can only be received and administered by veterinarians through the restricted distribution program because of the potential for human abuse and safety risks associated with its use in dogs.

WARNINGS:

Human Safety: Not for use in humans. Keep out of reach of children. Avoid unprotected contact with application site for 72 hours.

SECONDARY EXPOSURE TO FENTANYL: Strict adherence to the requirements of the RiskMAP and the INSTRUCTIONS FOR USE provided in this product insert is imperative in order to reduce the potential of secondary exposure to fentanyl from RECUVYRA treated skin.

Adult Human User Safety while handling and applying RECUVYRA in the Hospital:

Two trained staff for administration: Do not dispense RECUVYRA for administration at home by the pet owner. RECUVYRA should only be handled and administered to dogs by hospital staff specifically trained in its use. To prevent human adverse reactions or abuse, at least 2 trained administrators should be present during administration of RECUVYRA.

Protective covering: To prevent direct contact of RECUVYRA solution with human skin or mucous membranes when handling and/or applying the solution, wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat. To avoid inadvertent contamination of other humans or animals, remove and appropriately dispose of protective garments after RECUVYRA minimum drying time of 5 minutes.

Mucous membrane or eye contact during administration: Direct contact of RECUVYRA solution with the eyes, oral cavity or mucous membranes of dogs or humans could result in systemic, clinically relevant fentanyl concentrations. If accidental eye, oral or other mucous membrane contact is made during administration, flush the area with water and seek immediate medical attention.

Skin contact during administration: If human skin is accidentally exposed to RECUVYRA, wash the exposed area with soap and water and seek medical attention immediately. Accidental exposure could cause adverse reactions.

Drying time: Following application to the dog, allow a minimum drying time of 5 minutes. As a precaution, hospital staff responsible for handling the dog prior to, during, and after surgery, should wear gloves. All others (including owners) should avoid contact with the application site for 72 hours following application. Within this period, any part of the body that directly contacts the application site should be washed with soap and water and not placed in the mouth.

User Safety following discharge of the dog to the owner:

Adult exposure: Adults should avoid contact with the application site for 72 hours (3 days) following the application of RECUVYRA to the dog. Within this period, any part of the body that directly contacts the application site should be washed with soap and water and not placed in the mouth.

Child exposure: The dog should be isolated from children for 72 hours (3 days) from the time of RECUVYRA application to the dog.

If a child comes in direct contact with the dog within 72 hours (3 days) from the time of RECUVYRA application to the dog, the exposed **part of the child's body should not contact the child's mouth or eyes, and the area should be washed with soap and water.**

If a child's tongue comes in contact with the dog, or another part of the child's body comes in contact with the dog and is then placed in the mouth, it is possible for fentanyl to enter the bloodstream; this is a medical emergency and the child should be seen immediately by a physician.

Drug abuse, addiction and diversion of opioids: RECUVYRA contains fentanyl, a μ-opioid agonist and a Class II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and may be subject to misuse, and criminal diversion. RECUVYRA should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Physician information: Fentanyl is a μ (mu) opioid receptor agonist (50 mg/mL). The antidote for human exposure to RECUVYRA is an opioid reversal agent such as naltrexone or naloxone. In the case of an emergency, provide the physician with the package insert and Client Information Sheet.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that RECUVYRA, when used according to the label, is safe and effective for the control of pain associated with surgical procedures in dogs.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because the product is a long-acting, highly concentrated, schedule II opioid with a high

potential for human abuse. Adverse reactions could be significant and professional veterinary expertise is required to monitor safety in dogs.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.